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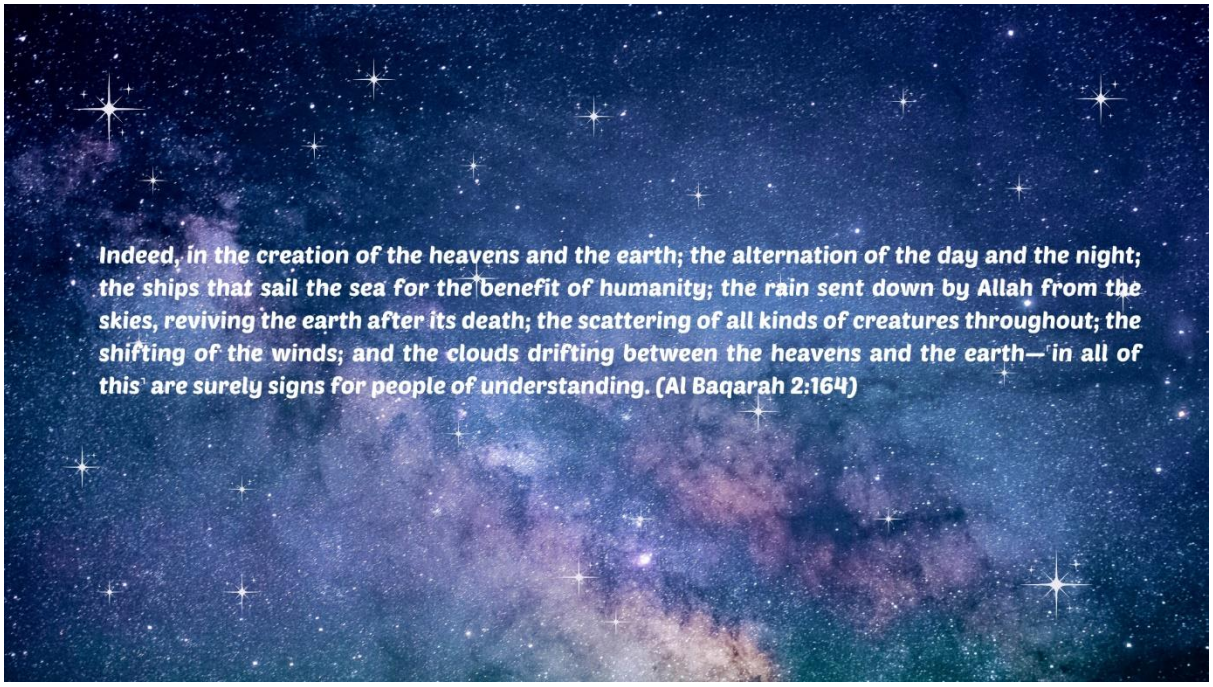
Journal of AI & Disease Data Set

Official Journal of Rawalpindi Medical University

AI-Driven Analysis of
Real-World Disease Data

Disclosure Statement

The Journal of AI & Disease Dataset (JAID) is the official journal of Rawalpindi Medical University (RMU). The articles published in this journal are based on real clinical patient data collected from three RMU-affiliated teaching hospitals: District Headquarters Hospital (DHQ), Holy Family Hospital (HFH), and Benazir Bhutto Hospital (BBH). JAID uses various artificial intelligence (AI) tools to help with writing, data analysis, and presentation of research. While the patient data used in all articles is real and clinically authentic, some parts of the written content or analysis are AI-assisted. RMU does not allow any material published in this journal to be copied, republished, or submitted to another journal or platform without prior written permission.


Indeed, in the creation of the heavens and the earth; the alternation of the day and the night; the ships that sail the sea for the benefit of humanity; the rain sent down by Allah from the skies, reviving the earth after its death; the scattering of all kinds of creatures throughout; the shifting of the winds; and the clouds drifting between the heavens and the earth—in all of this are surely signs for people of understanding. (Al Baqarah 2:164)

Editorial Policies
The Journal of AI & Disease Dataset (JAID)

Editorial Policies

The journal is dedicated to publishing scholarly articles in the field of Artificial Intelligence, with a particular focus on disease analysis and research using hospital and healthcare datasets. All manuscripts are prepared using various AI tools under careful human supervision and editorial oversight. The editorial team ensures the accuracy, relevance, originality, and academic integrity of the content. AI tools are used solely for content generation and are not recognized as authors of the articles. Each submission is reviewed to meet ethical standards, especially concerning healthcare data and research practices. The journal is committed to transparency and the responsible use of artificial intelligence in medical and health-related research.

Journal aims, scope and indexing

The Journal of AI & Disease Dataset (JAID) aims to promote high-quality research in the field of Artificial Intelligence, with a special focus on disease analysis and healthcare applications using hospital datasets. The journal encourages innovative and interdisciplinary research that applies AI techniques to real-world medical and clinical challenges.
The scope of JAID includes artificial intelligence, machine learning, deep learning, data analytics, medical informatics, and ethical AI practices. It publishes original research articles, review papers, and case studies that contribute to academic and practical advancements in AI.

Submission prerequisites and manuscript preparation

Manuscripts submitted to The Journal of AI & Disease Dataset (JAID) must be original, unpublished, and not under consideration elsewhere. All submissions should align with the journal's aims, particularly research involving Artificial Intelligence, disease analysis, and healthcare or hospital datasets. Authors/editors must ensure that ethical standards are followed, especially in the use of medical data, with proper anonymization and compliance where applicable.

Manuscripts should be prepared in clear and concise English with a logical structure, including title, abstract, keywords, introduction, methodology, results, discussion, and references. Proper citations from credible and verifiable sources are mandatory, and all references must be checked for accuracy. Figures, tables, and datasets should be clearly labeled and relevant to the study.

Authorship, acknowledgements and contributor statements

Authorship in The Journal of AI & Disease Dataset (JAID) is limited to individuals who have made significant intellectual or editorial contributions to the manuscript. Since manuscripts may be generated using AI tools, such tools are not recognized as authors. Human contributors are responsible for the accuracy, originality, ethical compliance, and final approval of the submitted work.
Acknowledgements should be used to recognize individuals, institutions, or organizations that provided support, resources, or guidance but do not meet the criteria for authorship. Any financial, technical, or institutional assistance should be clearly stated.
A contributor statement must be included, specifying the role of each contributor, such as conceptualization, data curation, editorial review, validation, and supervision. The use of various AI tools must be explicitly disclosed in this section to ensure transparency.

Research ethics, patient consent and data handling

The Journal of AI & Disease Dataset (JAID) requires that all research adhere to high ethical standards, particularly studies involving healthcare, disease analysis, and hospital datasets. Authors are responsible for ensuring that research is conducted in accordance with institutional, national, and international ethical guidelines.
For studies involving patient data, informed consent must be obtained where applicable, and the use of data should be approved by the relevant ethics committee or authority. All patient information must be properly anonymized to protect privacy and confidentiality.
Data handling practices must ensure accuracy, security, and responsible use of healthcare data. Authors must clearly state the source of datasets and confirm that data has been used solely for research purposes in compliance with ethical and legal requirements.

Peer review model, reviewer selection and standards

The Journal of AI & Disease Dataset (JAID) follows a **rigorous peer review process** to ensure the quality, accuracy, and integrity of published research. Manuscripts are evaluated based on originality, scientific merit, relevance to AI and healthcare applications, and adherence to ethical standards.

The journal employs a **single-blind editorial review model**, where reviewers remain anonymous to authors to encourage objective and unbiased evaluation. Reviewers are selected based on their expertise in AI, machine learning, healthcare analytics, and related fields, ensuring a thorough assessment of technical and methodological rigor.
Reviewers are expected to provide constructive feedback, identify methodological or ethical concerns, and verify the credibility of references and data sources. All reviews are conducted confidentially, and conflicts of interest must be disclosed to maintain transparency and integrity throughout the review process.

Editorial governance, independence and conflicts of interest

The Journal of AI & Disease Dataset (JAID) is governed by an editorial board responsible for maintaining the scientific quality, integrity, and ethical standards of all publications. The board oversees manuscript evaluation, policy enforcement, and strategic direction, ensuring that the journal meets its academic objectives.
The editorial team operates independently of commercial, institutional, or personal influences, making decisions based solely on the scholarly merit and relevance of submitted work. Authors, reviewers, and editors are required to disclose any potential conflicts of interest that could affect impartiality.
Any identified conflicts are carefully managed to maintain transparency and trust in the publication process. The journal prioritizes ethical governance, unbiased editorial decisions, and accountability in all aspects of manuscript handling and publication.

Corrections, expressions of concern, retractions and article removal

JAID is committed to maintaining the integrity and accuracy of the scientific record. If errors, inaccuracies, or ethical issues are identified post-publication, the journal may issue **corrections** to clarify or amend the content.
In cases where concerns arise about the validity, reliability, or ethical compliance of a publication, the journal may publish an **expression of concern** while an investigation is conducted. If serious misconduct, data fabrication, or significant ethical violations are confirmed, the article may be **retracted**, with a clear explanation provided to readers.
Articles may be **removed** in exceptional cases where content poses legal, ethical, or safety risks. All corrections, expressions of concern, retractions, and removals are documented transparently to uphold the trustworthiness of JAID and the scientific community.

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Manipulation of images, figures, or data to misrepresent results is strictly prohibited. Any adjustments to visual material must be clearly described and must not alter the scientific meaning. Violations of these standards may result in rejection, correction, or retraction of the article.

Use of artificial intelligence and similarity thresholds

The Journal of AI & Disease Dataset (JAID) recognizes the use of various artificial intelligence tools to assist in manuscript preparation, data analysis, or literature synthesis. Authors must **fully disclose the use of AI tools** in their work, specifying the role of AI and the extent of human oversight in content creation. AI tools are not considered authors, and human contributors remain responsible for the accuracy, originality, and ethical compliance of the manuscript

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The Journal of AI &Disease Data Set (JAID)provides a transparent mechanism for authors, reviewers, and readers to raise **appeals or complaints** regarding editorial decisions, peer review, or publication processes. Appeals should be submitted in writing to the editorial office with clear justification, and they will be reviewed by senior editors or an independent committee.
The journal takes **research misconduct** seriously, including plagiarism, data fabrication, ethical violations, or undisclosed conflicts of interest. All allegations are investigated thoroughly, maintaining confidentiality and fairness.
If misconduct is confirmed, appropriate actions may include corrections, retractions, sanctions, or reporting to relevant institutions. The procedures aim to protect the integrity of the scientific record while ensuring fairness and accountability for all parties involved.

Supporting materials, checklists and governance aids

The Journal of AI &Disease Data Set (JAID)provides authors, reviewers, and editors with a range of **supporting materials and checklists** to ensure the quality, transparency, and ethical compliance of submissions. These resources include manuscript preparation guidelines, data reporting templates, ethical compliance checklists, and AI usage disclosure forms.
Governance aids are provided to assist the editorial board in maintaining consistent review standards, managing conflicts of interest, and ensuring adherence to the journal's policies. Authors are encouraged to use these tools to improve manuscript completeness, clarity, and compliance with JAID editorial and ethical standards.

Disclaimer

JAID is a journal that publishes AI-generated reviews of medical research papers, case studies, and related content. The data used in these publications are collected from hospitals and other medical sources.
While JAID aims to provide accurate and reliable information, the content is AI-generated and may not always reflect complete clinical accuracy. JAID and its contributors do not assume responsibility for any medical decisions, treatments, or outcomes based on the content published in the journal.
All content is intended for informational and educational purposes only and should not be considered a substitute for professional medical advice, diagnosis, or treatment. Readers are advised to consult qualified healthcare professionals for any medical concerns.

Editorial Board

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Introduction to RMU- Disease Data Centre

The presence of a Disease Data Centre (DDC) within a medical university is a strategic asset that underpins research excellence, evidence-based clinical practice, and public health surveillance. Serving as the nucleus of information management, the RMU–DDC systematically collects, stores, and analyses patient-level data across multiple disease categories.

By bridging clinical observation with research infrastructure, the DDC enables faculty, postgraduate researchers, and public health professionals to extract actionable insights from real-world data — ultimately advancing patient care and medical knowledge.

Vision & Mission

Vision

To become a leading national repository of disease-specific patient data, empowering evidence-based medicine and health policy across Pakistan.

Mission

To systematically collect, manage, and analyse high-quality clinical data, supporting research, education, and improved patient outcomes at RMU and its allied hospitals.

Scope & Objectives

Comprehensive Data Repository	Systematic storage of patient records, lab data, and clinical outcomes across disease categories.
Evidence-Based Research	Supporting faculty and postgraduate students with curated datasets for high-quality research.
Precision Medicine	Enabling personalised treatment strategies through granular patient-level data analysis.
Streamlined Clinical Trials	Facilitating participant recruitment, follow-up, and data analysis for ongoing trials.
Quality Improvement	Tracking performance metrics and outcomes to drive continuous clinical improvement.
Multidisciplinary Collaboration	Uniting clinicians, researchers, and public health professionals around shared data resources.

Data Management Policy

Rawalpindi Medical University fully recognizes the value and importance of protecting personal, medical, and research-related information. The University is committed to transparency and accountability, demonstrating compliance with established regulatory principles.

A robust Research Data Management Policy governs all DDC activities. This policy ensures:

- Proper recording, maintenance, and secure storage of research data
- Controlled and appropriate access to sensitive clinical datasets
- Protection of intellectual property rights (IPR) in all research outputs

- Alignment with national and international data protection standards

Components of RMU–DDC

The DDC currently manages seven active disease-specific datasets. Collectively, these registries represent over 17,000 patient and sample records spanning nearly two decades of clinical activity.

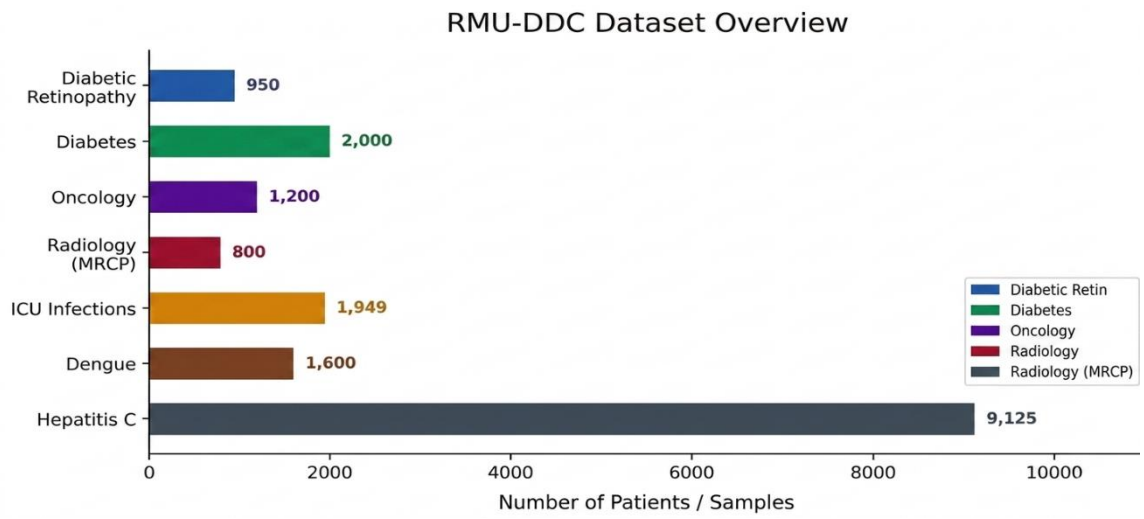

Figure 1 — Approximate patient/sample volumes across all DDC modules

1. Hepatitis C

9,125	18 yrs	2006–2024
Total Patients	Years of Data	Period

The hepatitis C virus (HCV) remains a significant public health concern in Pakistan, contributing to the growing burden of chronic liver disease, cirrhosis, and hepatocellular carcinoma. Effective monitoring requires systematic collection and longitudinal analysis of patient-level data.

Since 2006, the DDC has maintained a comprehensive HCV dataset comprising clinical, laboratory, and diagnostic records of 9,125 patients — the most extensive single-disease registry within the centre.

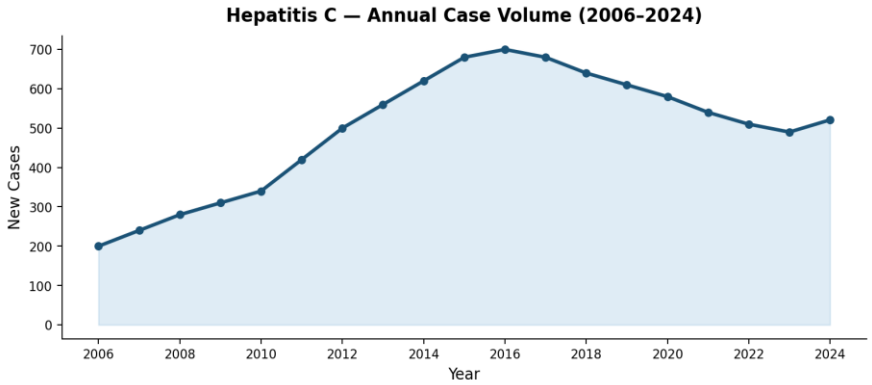

Figure 2 — Representative annual case volume trend, Hepatitis C dataset (2006–2024)

2. Dengue Fever

Dengue fever poses a recurring and significant health burden in Pakistan, particularly during seasonal outbreaks. Systematic data collection is critical for understanding disease trends, guiding patient management, and shaping public health interventions.

The DDC Dengue registry captures:

- Diagnostic tests: NS1 antigen, IgM and IgG antibody serology
- Ultrasonographic findings and day of illness (DOI) at admission
- Comorbid conditions: DM, HTN, Hepatitis B/C, COPD, asthma, IHD, CVA

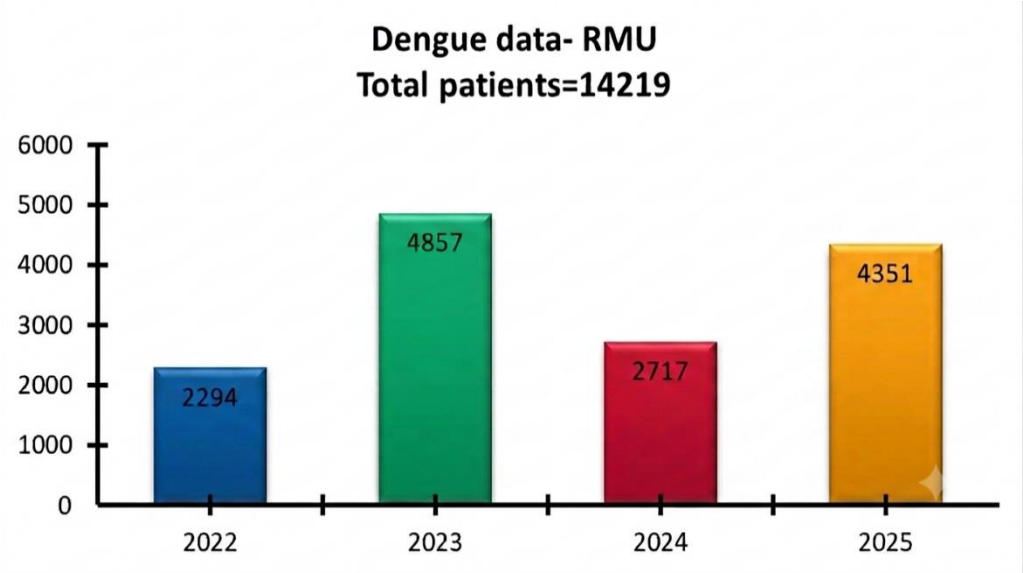

Figure 3: Total number of cases in Dengue dataset

3. ICU Infections

The increasing prevalence of multidrug-resistant organisms (MDROs) in critical care settings presents a serious challenge to patient safety. As of September 2024, the dataset includes 1,949 microbiological samples collected from ICU patients since December 2019.

Sample distribution across ward types:

CCU	MICU	NHDU	NICU	PHDU	PICU	SICU
194	777	18	166	127	431	236

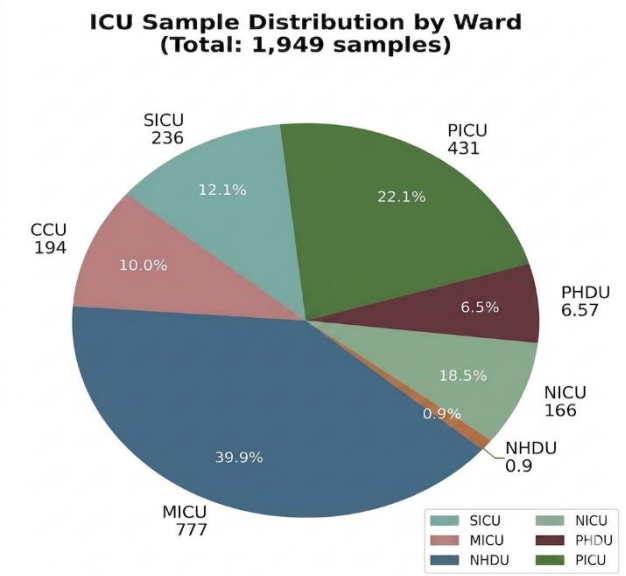

Figure 4 — ICU sample distribution by ward type (n = 1,949)

The dataset documents patient gender, specimen types, isolated organisms, and antibiotic susceptibility profiles enabling evidence-based antimicrobial stewardship.

4. Radiology (MRCP)

Magnetic Resonance Cholangiopancreatography (MRCP) is a non-invasive imaging modality crucial for diagnosing hepatobiliary and pancreatic disorders. The DDC Radiology module curates MRCP findings to support diagnostic research and outcome analysis.

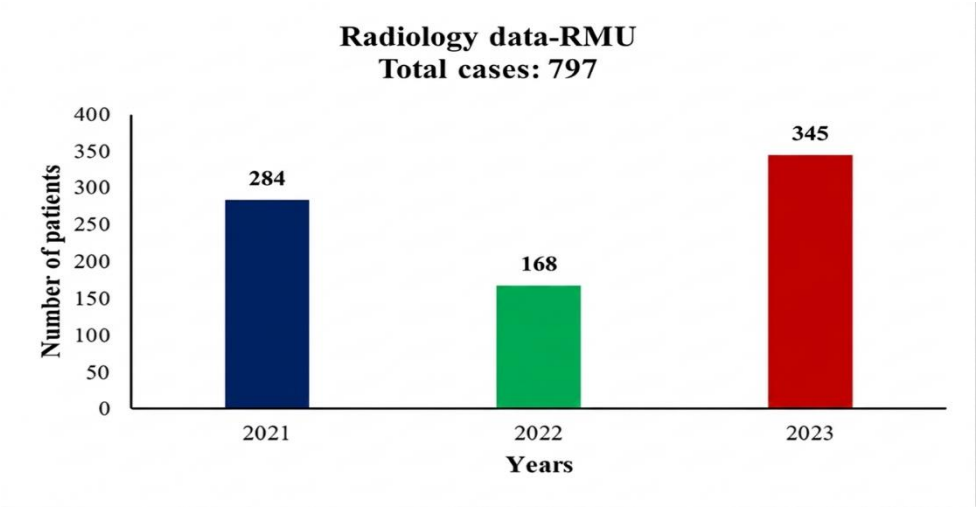

Figure 5 — Radiology (MRCP) dataset summary chart

5. Oncology

Cancer surveillance plays a pivotal role in understanding disease burden, planning patient care, and informing public health policy. The RMU Oncology registry tracks diagnosis, staging, treatment pathways, and outcomes across major cancer types.

The bar chart illustrates the year-wise distribution of cancer patients from 2022 to 2025. In 2022, the number of patients was 121, representing the lowest value. A sharp increase followed in 2023, with the number of cases peaking at 279. However, in 2024, the patient count declined markedly to 183, indicating a reduction after the previous year's surge. In 2025, the number of cancer patients rose slightly again to 203. Overall, the data demonstrate a fluctuating trend, with a significant rise between 2022 and 2023, a decline in 2024, and a modest increase in 2025.

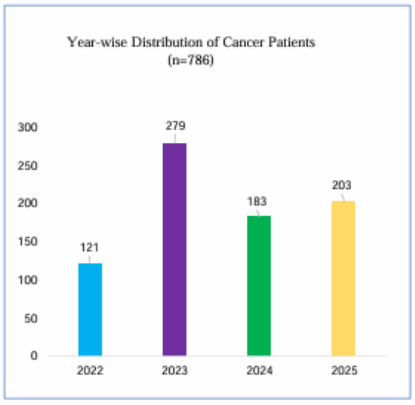

Figure 6 — Oncology dataset distribution by cancer type

6. Diabetes

Effective diabetes management depends on systematic collection of clinical, lifestyle, and complication-related patient data. The RMU Diabetes Registry provides a longitudinal view of glycaemic control and complication rates.

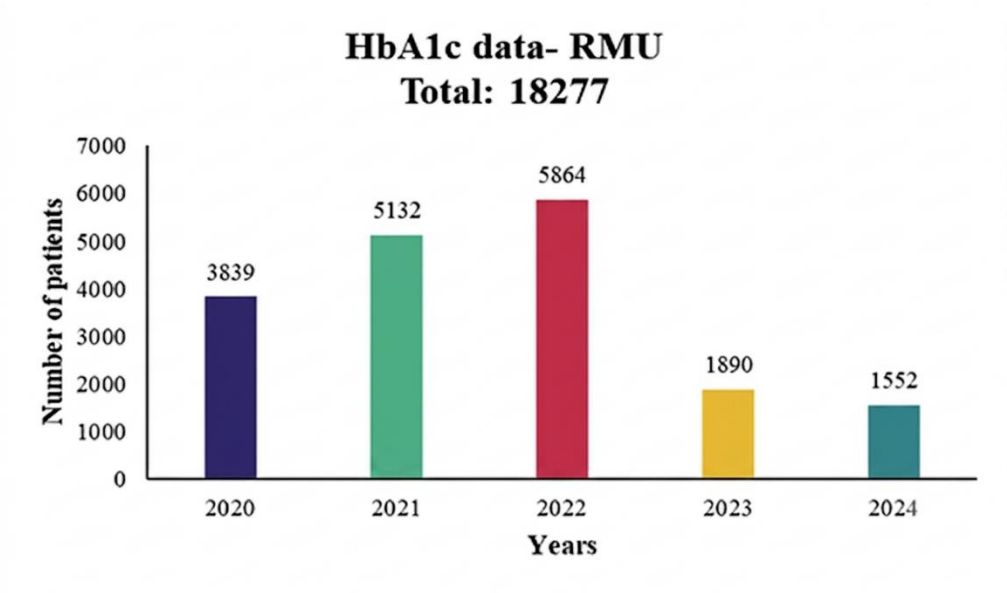

Figure 7 — HbA1c dataset summary chart

7. Diabetic Retinopathy

The Diabetic Retinopathy database compiles clinical and demographic information on patients with retinal disorders. It records visual acuity, disease severity grading, comorbidities, treatment interventions, and outcomes — supporting early detection strategies and evidence-based management.

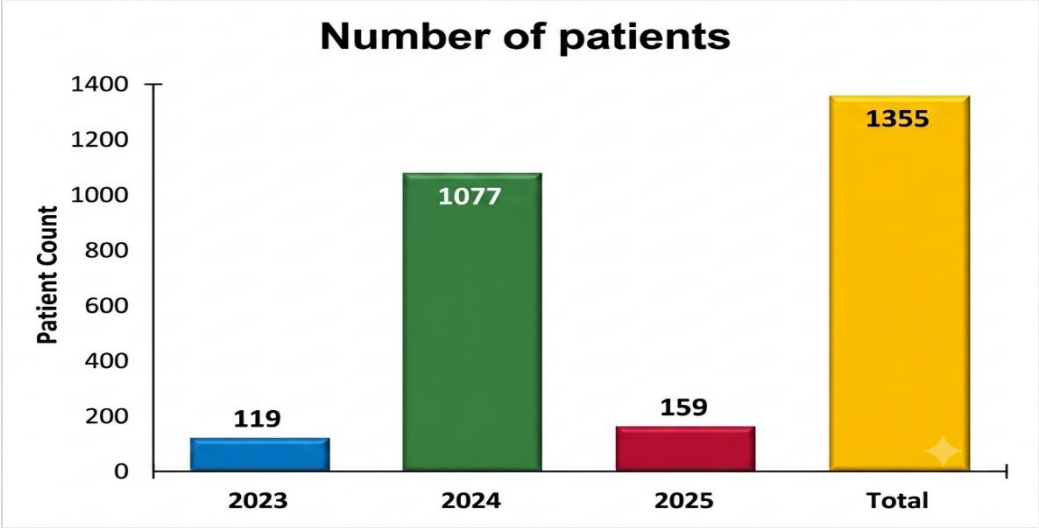

Figure 8 — Diabetic Retinopathy dataset summary chart

Conclusion

The RMU Disease Data Centre represents a sustained and growing commitment to data-driven medicine at Rawalpindi Medical University. Spanning seven disease modules and nearly two decades of patient records, the DDC has established itself as a cornerstone of clinical research and academic scholarship at RMU and its allied hospitals.

The datasets maintained within the DDC are actively utilized for research publications and contribute directly to the Journal of AI & Disease (JAID), RMU's dedicated platform for disseminating data-driven clinical research. Through JAID, findings derived from these registries reach clinicians, researchers, and policy-makers both nationally and internationally, amplifying the translational impact of the data collected.

All patient data held within the DDC has been collected in full accordance with ethical research standards. Informed consent was obtained from all patients prior to inclusion in any dataset, and all records are anonymised and stored securely in compliance with RMU's Research Data Management Policy. Patient privacy, confidentiality, and autonomy remain central to the operational principles of the Disease Data Centre.

As the DDC continues to expand its scope, it is poised to play an increasingly vital role in shaping evidence-based healthcare delivery, supporting postgraduate education, and advancing Pakistan's contribution to global medical research.

PREAMBLE

Why Rawalpindi Medical University needs Journal of AI & Disease Data set (JAID)?

In alignment with Rawalpindi Medical University Vision 2017–2025, which prioritizes research excellence, innovation, digital transformation, and societal impact, the Journal of AI and Disease Data (JAID) is proposed as a strategic academic initiative to strengthen RMU's leadership in data-driven healthcare research.

RMU's vision emphasizes the integration of modern technologies to improve healthcare delivery, medical education, and public health outcomes. Artificial Intelligence (AI) and disease data analytics are central to this transformation, enabling predictive diagnostics, precision medicine, intelligent disease surveillance, and evidence-based health policy. JAID will provide a dedicated, peer-reviewed platform to promote interdisciplinary research that connects clinical medicine, public health, biomedical sciences, and digital technologies, with a particular focus on diseases relevant to Pakistan and the region.

Through high-quality publications, JAID will enhance RMU's national and international research visibility, encourage collaborative research, support institutional digital initiatives, and contribute to capacity building in emerging health technologies. The journal will thus serve as a key instrument in achieving RMU's strategic goals under Vision 2025.

Aim and Scope of the Journal

The Journal of AI and Disease Data (JAID) aims to advance high-quality research on the application of Artificial Intelligence and data analytics in understanding, prevention, diagnosis, and management of diseases. The journal provides a credible academic platform for clinicians, researchers, data scientists, and postgraduate students to disseminate innovative and interdisciplinary research integrating medical sciences, public health, and AI technologies. JAID particularly encourages data-driven studies addressing local, national, and regional disease burdens, while strengthening RMU's research visibility, academic impact, and international collaborations. The journal also supports RMU's digital health, innovation, and research governance initiatives in alignment with Vision 2017–2025.

AI Journal and Its Usefulness for RMU

Rawalpindi Medical University (RMU) needs a dedicated Artificial Intelligence journal to respond to the rapidly evolving role of data-driven technologies in healthcare, medical education, and public health. As disease surveillance, diagnostics, and health system management increasingly rely on large-scale data and AI-based analytics, RMU requires an academic platform that captures, organizes, and disseminates such research in a focused and credible manner. The **JAID** will address this need by providing a specialized outlet for high-quality research relevant to local and regional disease patterns, which are often underrepresented in international journals.

JAID will be useful in strengthening RMU's research ecosystem by promoting interdisciplinary collaboration among clinicians, public health experts, and data scientists, improving research visibility and citations, and supporting evidence-based healthcare solutions. The journal will also enhance faculty and postgraduate research capacity, contribute to policy-relevant disease data analysis, and align with RMU's digital transformation initiatives under Vision 2017–2025. Ultimately, JAID will position RMU as a national leader in AI-driven medical research and innovation.

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Global Cancer Trends 2024–2026

Epidemiology, Emerging Therapeutics & AI Integration

1. Global burden at a glance

In 2026, the American Cancer Society estimates more than 2.1 million new cancer diagnoses in the United States (approximately 5,800 cases daily). Globally, an estimated 23.6 million new cancer cases and 9.83 million cancer deaths were recorded in 2021 (GBD Study). Counterbalancing these concerns, for the first time in history, the five-year relative survival rate for all cancers combined has reached 70% among patients diagnosed 2015–2021 in the US, and cancer mortality has declined 34% since 1991, representing 4.8 million lives saved.

2.1M+	23.6M	9.83M	70%	34%
New US cancer diagnoses (2026 est.)	Global new cancer cases (GBD 2021)	Global cancer deaths (2021)	US 5-year survival (all cancers, 2015–21)	Decline in US mortality since 1991
↑ ~5,800/day	↑ 2.7%/yr	↑ 1.6%/yr	Historic milestone	4.8M lives saved

2. Leading cancer types — United States 2026 (estimated new cases)

In men, the most common malignancies remain prostate, lung, and colorectal cancers. In women, breast, lung, and colorectal cancers dominate. Troubling trends include rising breast cancer incidence in women under 50, more men diagnosed with advanced-stage prostate cancer, and a persistent increase in colorectal cancer in adults under 50.

Cancer type	Men (est.)	Women (est.)	Key 2026 trend
Prostate	288,000	—	Most common in men
Breast	—	316,000	Incidence rising in <50
Lung	120,000	130,000	Leading cause of cancer death
Colorectal	79,000	72,000	Rising in adults <50
Melanoma	59,000	38,000	Significant incidence
Prostate†	—	—	↑ Advanced-stage diagnoses

† Concerning trend of advanced-stage diagnosis at presentation in 2026. Source: Siegel et al. [1]; ACS 2026 [2].

3. Global cancer incidence & mortality by world region — Globocan 2022

Age-standardized rates (ASR) per 100,000 population reveal significant disparities. Africa records the highest mortality-to-incidence ratio (MIR 0.51), reflecting challenges in early detection, access to treatment, and health infrastructure. Eastern Asia shows high mortality despite moderate incidence, driven by gastric and liver cancer burden. High-income regions (Northern America, Australia/NZ) report the highest incidence due to greater detection capacity, but lower MIRs.

World region	Incidence ASR*	Mortality ASR*	Notable context
Northern America	362	103	High HDI; strong screening infrastructure
Australia / NZ	347	95	High HDI; early detection programs
Europe	290	108	Variation across sub-regions
Eastern Asia	204	122	Gastric & liver cancer burden

World region	Incidence ASR*	Mortality ASR*	Notable context
Latin America	169	89	Cervical cancer persistent issue
South-East Asia	142	95	Limited registry coverage
South-Central Asia	103	72	Oral & oesophageal high
Africa	112	85	Highest mortality-to-incidence ratio

** ASR = Age-standardised rate per 100,000. Source: WCRF/IARC GLOBOCAN 2022 [4].*

4. Emerging therapeutics & treatment landscape 2025–2026

Key trends shaping cancer treatment in 2025–2026 include advances in immunotherapy, AI-integrated care, and precision oncology. The table below summarizes the most impactful developments reported by ACS, AACR, City of Hope, and Van Andel Institute.

Trend / domain	Detail	Direction
CAR-T & armored T-cells	IL-18, IL-12, IL-15 enhanced constructs; active in lymphoma & blood cancers (AACR IO 2026)	**↑ Active**
Immunotherapy trials	6,000+ active ClinicalTrials.gov immunotherapy studies as of 2025	**↑ Growing**
Breast cancer incidence	Rising especially in women under 50; early detection and AI screening critical	**↑ Concern**
Prostate — advanced stage	More men in 2026 being diagnosed at advanced, less curable stages	**↑ Concern**
Colorectal in under-50s	Increasing trend in younger adults; unclear etiology, warrants screening expansion	**↑ Rising**
Digital pathology & multi-omics	AI standard for extracting HER2, BRCA, MSI from routine H&E slides (ASCO 2025)	**↑ Active**
Agentic AI in surgery	AI-guided robotic systems reducing complications & recovery time (City of Hope, 2026)	**↑ Emerging**
Survival milestone	5-year all-cancer survival hits 70% for first time in US history (ACS 2026)	**✓ Positive**

5. AI integration across the oncology pipeline

Artificial intelligence is now embedded across every stage of oncology — from screening through to surgical intervention. City of Hope (2026) projects that AI-powered patient-matching tools could improve clinical trial enrolment rates by up to 26%. Deep learning models trained on CT radiomics achieved AUC 0.81 for predicting immunotherapy response in advanced NSCLC (JAMA Oncology 2025). Digital pathology AI can extract HER2, BRCA, and MSI biomarkers from routine H&E-stained whole slide images (ASCO 2025).

#	Pipeline stage	Current evidence & application
1	**Screening & Detection**	AI imaging (CT, MRI, mammography) in lung, breast, brain, prostate, colorectal cancers
2	**Biomarker Discovery**	Multi-omics AI; HER2, BRCA, MSI extraction from H&E slides; digital pathology
3	**Drug Discovery**	AI accelerates preclinical pipelines; faster clinical trials; improved drug availability

#	Pipeline stage	Current evidence & application
4	**Patient Matching**	+26% projected trial enrolment via AI-powered patient-matching tools (City of Hope, 2026)
5	**Response Prediction**	AUC 0.82 for immunotherapy response; deep learning on CT radiomics, genomics, cytokines
6	**Agentic AI Surgery**	AI-guided robotic systems; reduced complications; shorter recovery (City of Hope, 2026)

6. AI performance in cancer-specific tasks — evidence summary

The following table summarizes six published AI applications in oncology, including AI method, performance metric, and evidence level. Cells are colour-coded by impact strength: blue = established/moderate, amber = emerging/validated, red = highest projected or demonstrated impact, teal = positive milestone.

Application	Cancer type	AI method	Performance	Evidence level
Recurrence risk prediction	Breast	Deep learning (multi-omics)	**Outperforms standard tools**	Phase II RCT (ECOG-ACRIN / Caris, 2025)
Immunotherapy response	Lung NSCLC	Deep learning (CT radiomics)	**AUC 0.81**	Prospective cohort (JAMA Oncol, 2025)
Survival prediction	Melanoma	ML ensemble (36 studies, 75 models)	**c-index 0.82**	Systematic review & meta-analysis
Pathology biomarker extraction	Multiple	Digital pathology (H&E + WSI)	**HER2, BRCA, MSI from slides**	ASCO 2025 highlights
CAR-T efficacy prediction	Blood cancers	ANN image segmentation	**Correlates with clinical response**	NCT00881920 translational study
Clinical trial enrolment	All cancers	AI patient-matching tools	**+26% projected increase**	City of Hope / 2026 projection

AUC = area under ROC curve; c-index = concordance index; WSI = whole slide image; NSCLC = non-small cell lung cancer; MIR = mortality-to-incidence ratio.

7. Breast cancer global projections to 2050 — Globocan (freihat et al., 2025)

Using Average Annual Percent Change (AAPC) data from 2018–2022, Freihat et al. project global breast cancer cases exceeding 6 million by 2050. Asia will experience the most significant rise (2.0 million cases), while Africa, despite lower absolute numbers, will bear the highest mortality-to-incidence ratio (MIR 0.35 vs Europe 0.20). These projections emphasise the urgent need for early detection infrastructure in low-to-middle-income countries (LMICs).

Region	Proj. cases (2050)	Proj. deaths (2050)	MIR	Notes
Asia	2,000,000	484,468	0.25	Highest projected absolute rise
Africa	1,118,000	390,695	0.35	Highest MIR; limited access
Europe	800,000	160,000	0.20	Better survival outcomes
N. America	550,000	88,000	0.16	Strong early-detection systems
Latin America	480,000	120,000	0.25	Moderate access disparities

Region	Proj. cases (2050)	Proj. deaths (2050)	MIR	Notes
Oceania	80,000	14,000	0.18	Low MIR; good coverage

MIR = Mortality-to-Incidence Ratio. Projected values based on AAPC 2018–2022 applied to demographic projections. Source: Freihat et al. [5].

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Original Article

Geographic Access, Financial Barriers, Healthcare-Seeking Delays, and Referral Pathways in Liver Cancer: A Health Systems Analysis from the RMU Disease Data Centre, 2026

Abstract

Background: Liver cancer outcomes in Pakistan are adversely shaped not only by tumor biology but by structural factors including geographic inaccessibility, financial toxicity, prolonged healthcare-seeking delays, and fragmented referral networks. Despite the abundance of real-world clinical data in tertiary oncology registries, health systems analysis of liver cancer patients in Pakistan are virtually absent from the published literature.

Objectives: To describe and quantify geographic origin, symptom-to-presentation delay, referral source and pathway, financial barriers to treatment, co-morbidity burden, and patterns of care disruption among liver cancer patients registered at the RMU Oncology Clinic during the first quarter of 2026.

Methods: Retrospective analysis of 16 liver malignancy cases (HCC n=12; biliary/GB malignancy n=4) from the RMU Disease Data Centre registry, January–April 2026. Variables included patient domicile (mapped by district), referral source, documented symptom duration, treatment access, financial support documentation, outward referral destination, and co-morbidities. Content analysis was applied to free-text clinical notes.

Results: Patients originated from 7 districts spanning a geographic radius of 200 km, with 62.5% residing outside Rawalpindi. Majority (50%) presented with symptom duration exceeding one month before reaching tertiary care. Three patients required state welfare (Bait ul Mal/BTM) or charitable financing for medicines; four received only best supportive care (BSC), of whom financial barrier was implicated in two. Outward referral was required in 56.3% of cases (NORI, PIMS, CMH) due to limited specialist infrastructure at RMU/HFH. HCV and tobacco use — both preventable/modifiable risk factors — were present in over 50% of assessable patients. Two patients were lost to follow-up, likely due to communication and logistical barriers.

Conclusions: This health systems analysis reveals that liver cancer management at HFH-RMU is constrained by a convergence of geographic distance, financial toxicity, diagnostic delays, and an incomplete local care continuum. Targeted interventions — including district-level HCC surveillance, subsidized TKI access, in-house TACE capacity, and a dedicated multidisciplinary liver tumor board — are urgently required.

Keywords: *Liver cancer; health systems; financial barriers; geographic access; referral pathways; HCC surveillance; Pakistan; Rawalpindi; treatment gap; health equity*

1. Introduction

The global burden of hepatocellular carcinoma (HCC) is disproportionately concentrated in low- and middle-income countries (LMICs), where structural inequities in healthcare access compound the biological aggressiveness of the disease [1]. In Pakistan, liver cancer represents a major oncological burden on a background of endemic hepatitis C (HCV prevalence 4.7–6.7%) and hepatitis B virus (HBV), tobacco use, and rapidly rising rates of metabolic risk factors including diabetes and obesity [2,3]. Yet the academic literature on liver cancer in Pakistan has remained predominantly clinical and epidemiological, with virtually no published data on the health systems dimensions of this disease: how far patients travel, what delays they endure, who finances their care, and where they are routed after initial oncological consultation.

The concept of the "treatment gap" — the difference between the burden of cancer and the proportion receiving guideline-recommended treatment — is particularly relevant to HCC in LMICs. Globally, over 70% of HCC patients in resource-constrained settings present with advanced disease, a statistic driven as much by health system failure as tumor biology [4]. Financial toxicity — defined as the adverse financial impact of cancer and its treatment is increasingly recognized as a driver of poor outcomes, treatment non-adherence, and treatment abandonment in South Asian oncology settings [5].

The RMU Disease Data Centre (DDC) at Holy Family Hospital (HFH) offers a unique opportunity to examine these health systems dimensions of liver cancer from a real-world, registry-based perspective. This study focuses specifically on the structural and socioeconomic factors governing the care trajectory of liver cancer patients in the Rawalpindi–Islamabad catchment area, complementing a companion paper (Volume 2, RMU DDC Journal) which reported on the clinicopathological profile of the same cohort.

2. Materials and Methods

2.1 Study Setting and Data Source

Holy Family Hospital (HFH), the primary clinical platform of Rawalpindi Medical University, serves as the main public-sector tertiary care and oncology referral centre for Rawalpindi District and a wider catchment area encompassing Attock, Chakwal, Jhelum, Mianwali, and Azad Jammu & Kashmir (AJK). The RMU DDC maintains a prospective oncology registry capturing patient registration details, referral source, clinical notes (including symptom history and financial documentation), treatment plans, and follow-up outcomes.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

2.2 Patient Selection

All 16 liver malignancy patients (HCC n=12; cholangiocarcinoma n=1; gallbladder CA with hepatic infiltration/neuroendocrine carcinoma n=3) registered during January 1 – April 14, 2026 were included. This is the same cohort as the companion clinicopathological study but is analyzed here exclusively through a health systems lens.

2.3 Variables Extracted

For each patient, the following health systems variables were extracted: (i) district of domicile (from address/CNIC); (ii) estimated distance from HFH, Rawalpindi (based on district HQ road distance); (iii) referral source (self, THQ/DHQ, NORI, CMH, HFH internal department); (iv) symptom-to-presentation interval, derived from structured history documented in clinical notes; (v) financial access category (self-funded, BTM/Bait ul Mal support, charitable/other, financial barrier to treatment); (vi) outward referral destination (NORI, PIMS, CMH, HCC clinic, managed locally); (vii) documented co-morbidities and modifiable risk factors; (viii) follow-up outcome (completed, lost to follow-up, expired, referred out).

2.4 Analytical Approach

Descriptive statistics with frequency counts and proportions were used. For geographic analysis, patients were mapped to their district of origin and estimated distance to HFH calculated using standard road distance estimates. Symptom-to-presentation delay was estimated from free-text clinical notes using explicit time references (e.g., “upper abdominal pain for 1.5 months”; “symptoms since 3 months”). Financial toxicity was assessed using an adapted framework from the literature [5,6].

3. Results

3.1 Geographic Distribution and Catchment Area

Liver cancer patients originated from 7 districts spanning the northern Punjab–AJK region (Figure 1). The largest single group came from Rawalpindi city itself (n=5, 31.3%), but 10 patients (62.5%) travelled from outside the district. Attock district contributed the largest out-of-district contingent (n=4, 25.0%), followed by AJK (Kotli/Hatyan Bala; n=2, 12.5%) and Chakwal (n=2, 12.5%). Single cases were documented from Islamabad, Jhelum, and Mianwali. Estimated road distances from HFH Rawalpindi ranged from under 5 km (Rawalpindi city) to over 200 km (Hatyan Bala, AJK). The majority (68.8%) of patients residing outside Rawalpindi relied on public or informal transport with no accompanying palliative travel support.

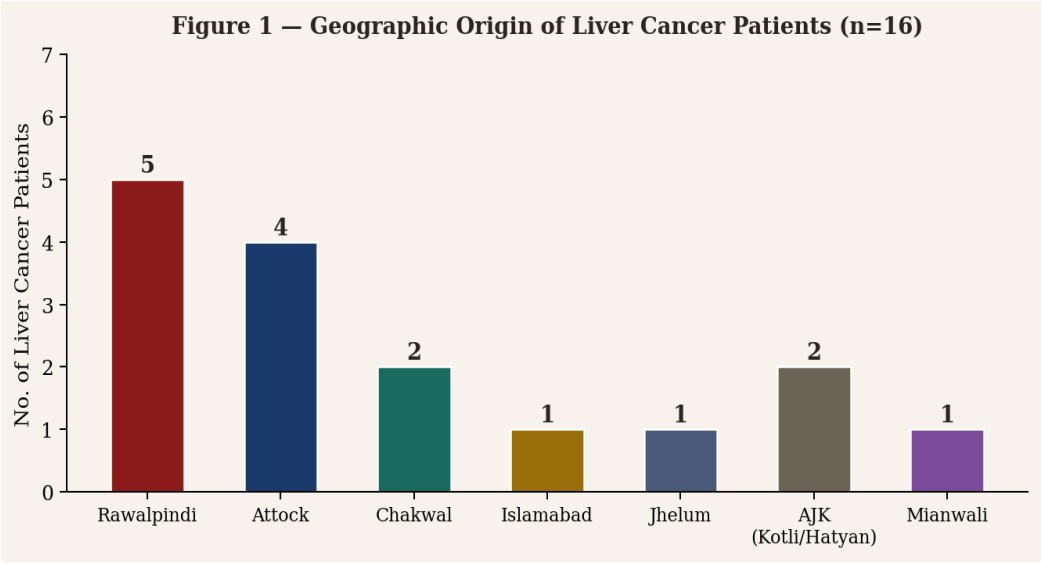

Figure 1 — Geographic Origin of Liver Cancer Patients by District (n=16), RMU Disease Data Centre, Jan–Apr 2026

Table 1 — Geographic Origin, Estimated Distance, and Travel Characteristics of Liver Cancer Patients

Reg No.	District	Est. Distance (km to HFH)	Residence Type	Remarks
UOC-915	Attock	55	Rural (Hassan Abdal)	
UOC-916	Attock	90	Rural (Pindi Gaib)	
UOC-918	Rawalpindi	12	Peri-urban	
UOC-931	Attock	60	Town (Taxila area)	
UOC-940	Jhelum	85	Rural (Pind Dadan Khan)	
UOC-945	Rawalpindi	5	Urban	
UOC-969	Chakwal	70	Town	

Reg No.	District	Est. Distance (km to HFH)	Residence Type	Remarks
UOC-973	Rawalpindi	8	Urban	
UOC-975	Rawalpindi	5	Urban	
UOC-997	AJK (Hatyan Bala)	210	Remote Rural	Longest travel distance
UOC-1001	Sadhonti (Chakwal)	75	Rural	
UOC-1005	Rawalpindi (Kallar Syedan)	40	Peri-urban	
UOC-1007	Rawalpindi	7	Urban	Post-HCV treatment
UOC-1019	Mianwali	160	Rural (Mianwali)	Phone unreachable
UOC-1023	Rawalpindi	6	Urban	
UOC-1029	Islamabad	15	Urban	

Est. Distance = estimated road distance from patient's stated locality to HFH, Rawalpindi. AJK = Azad Jammu & Kashmir.

3.2 Referral Sources and Entry Points into Oncology Care

The routes by which patients accessed the RMU Oncology Clinic were heterogeneous (Figure 2). Self-referral or self-presentation (walk-in) was the mode of entry for 5 patients (31.3%). Four patients (25.0%) were referred from THQ (Tehsil Headquarters) or DHQ (District Headquarters) hospitals, representing the intermediary tier of Pakistan's public healthcare pyramid. CMH (Combined Military Hospital) Rawalpindi referred three patients (18.8%), while two patients were referred from NORI (Nuclear Medicine, Oncology & Radiotherapy Institute), Islamabad — themselves a tertiary oncology center. One patient was referred from the HFH Gastroenterology department, reflecting appropriate intra-hospital triage.

The presence of NORI-referred patients at HFH-RMU — a reverse referral from a specialist cancer institute to a teaching hospital — highlights the role of HFH as a diagnostic and workup platform when NORI lacks specific investigative capacity or local specialist input. This bidirectional flow is a notable feature of cancer care navigation in the Rawalpindi–Islamabad corridor.

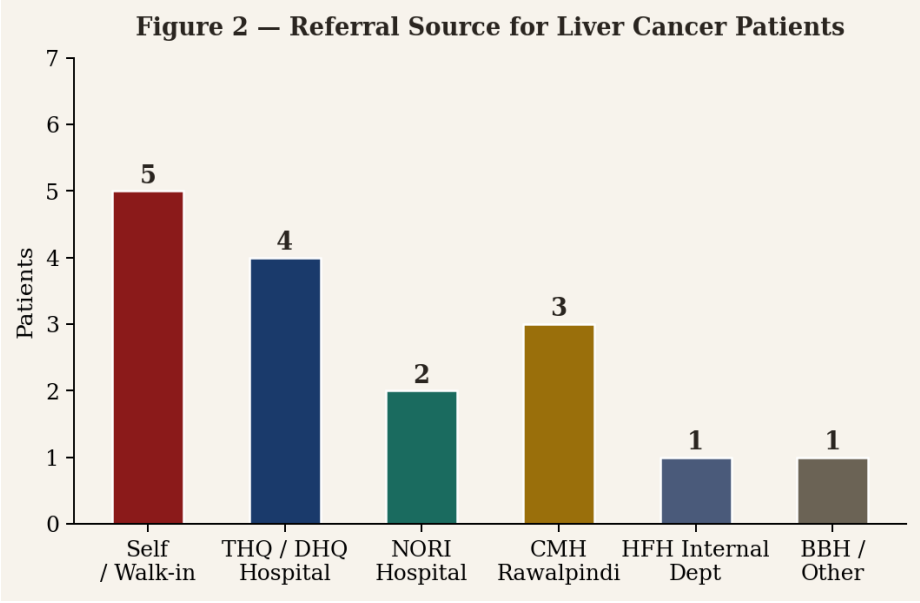

Figure 2 — Referral Source (Entry Pathway) for Liver Cancer Patients at RMU Oncology Clinic (n=16)

3.3 Healthcare-Seeking Delay: Symptom-to-Presentation Interval

Symptom duration prior to reaching the RMU Oncology Clinic was extractable from structured clinical histories in 14 of 16 patients (87.5%) (Figure 3). The most common documented symptom-to-presentation interval was 1–3 months (n=7, 50.0% of assessable cases), meaning the majority of patients had symptoms for at least one month before accessing tertiary oncology care. Three patients (21.4%) had documented symptoms exceeding 3 months, including one (UOC-1004) with 3 months of upper abdominal pain and one (UOC-1005) with "chronic dyspepsia" attributed to non-malignant causes. Only one patient (7.1%) presented within two weeks of symptom onset, and this was a patient already under follow-up for another condition.

These delays are consistent with published data from other South Asian settings. In a systematic review by Tran et al. [7], median patient delay to seeking oncology care in LMICs was 3 months for hepatobiliary cancers. Contributing factors documented in our cohort included: prior attribution of symptoms to

peptic disease or hepatitis (noted in 3 patients), prior management at primary care facilities without oncological imaging (THQ-referred patients), financial constraints delaying investigation, and remote rural domicile with limited access to radiology.

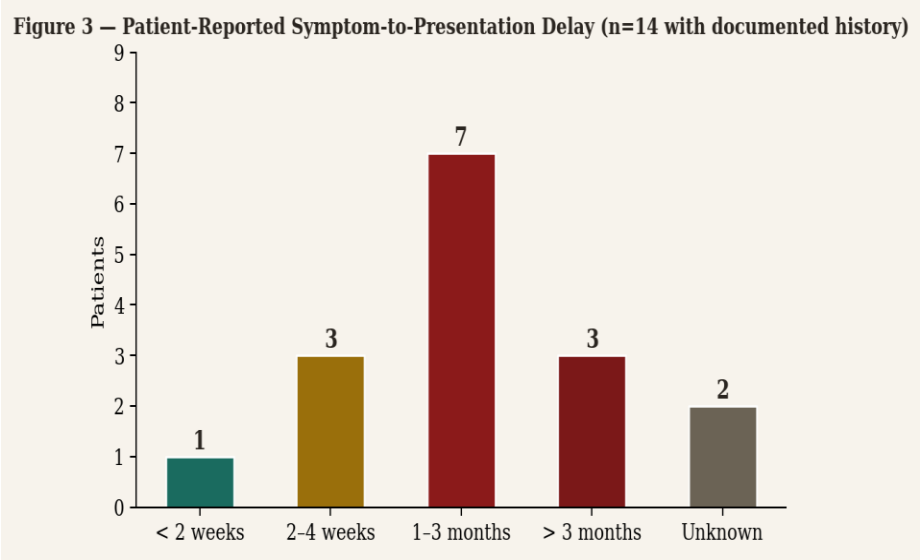

Figure 3 — Estimated Symptom-to-Presentation Delay in Liver Cancer Patients (n=14 with documented symptom history)

Table 2 — Documented Symptom Duration, Prior Treatment, and Factors Contributing to Delay (n=14 assessable cases)

Reg No.	Symptom Duration	Prior Attribution/Care	Possible Delay Factors
UOC-916	Unknown	Previous NORI treatment	Disease progression on treatment
UOC-931	> 1 month	THQ Taxila referral	Prior primary care management
UOC-940	> 1 month	Self-referred	Financial delay; rural domicile
UOC-945	Unknown	Self-referred	Attributed to hepatoma initially
UOC-973	> 1 month	BBH Hospital	Delay at secondary level; MRI not possible (metallic teeth)
UOC-975	> 1 month	Self-referred	Financial barrier; BTM support required
UOC-997	> 1 month	Self-referred	Remote rural AJK; AFP/CT not done for > 6 weeks after registration
UOC-1001	Unknown	CMH referral	HCV treated but not surveilled; delayed HCC detection
UOC-1004	3 months	HFH ER referral	Symptoms misattributed; prior cholecystectomy history
UOC-1005	> 1 month	THQ Kallar Syedan	HCV detected 1 month prior to HCC diagnosis; no surveillance
UOC-1007	2 weeks	HFH DMS referral	HTN-related visit incidentally revealed liver mass
UOC-1019	Unknown	Self-referred	Phone unreachable; follow-up lost
UOC-1023	Unknown	Self-referred	High creatinine delaying CT; workup in progress
UOC-1029	2 months	Gastro OPD referral	Known HCV treated; no HCC surveillance; delayed presentation

BBH = Benazir Bhutto Hospital Rawalpindi; BTM = Bait ul Mal (state welfare program); DMS = Deputy Medical Superintendent.

3.4 Financial Toxicity and Treatment Access

Financial barriers were a prominent theme across multiple patient records (Figure 4). Three patients (18.8%) explicitly required the Bait ul Mal (BTM) welfare scheme or charitable institutional funding to access medicines: UOC-975 (PKR 12,000 provided for lenvatinib), UOC-997 (lenvatinib 4 mg × 2 OD initiated through BTM, with a delay of 6–7 weeks from registration to treatment initiation due to procurement logistics), and UOC-973 (BTM process initiated for lenvatinib 8 mg/day). This represents a minimum estimate, as financial constraints were implicit rather than explicit in several additional records.

Four patients received best supportive care (BSC) as the primary management strategy; financial barrier was a documented or probable contributing factor in at least two of these (UOC-940 and UOC-975). Lenvatinib, the standard first-line TKI for unresectable HCC, costs approximately PKR 18,000–28,000 per month in Pakistan, representing approximately 1.5–2.5 times the monthly income of rural agricultural workers in northern Punjab. The REFLECT trial demonstrated lenvatinib's non-inferiority to sorafenib with superior PFS (7.4 vs 3.7 months) and ORR (24.1% vs 9.2%) [8], but this benefit is inaccessible to a substantial proportion of the HFH patient population. Atezolizumab plus bevacizumab (IMbrave150) and durvalumab plus tremelimumab (HIMALAYA)

— the current first-line immunotherapy standards [9,10] — were not initiated in any patient in this cohort, almost certainly due to cost: monthly immunotherapy costs exceed PKR 300,000–500,000.

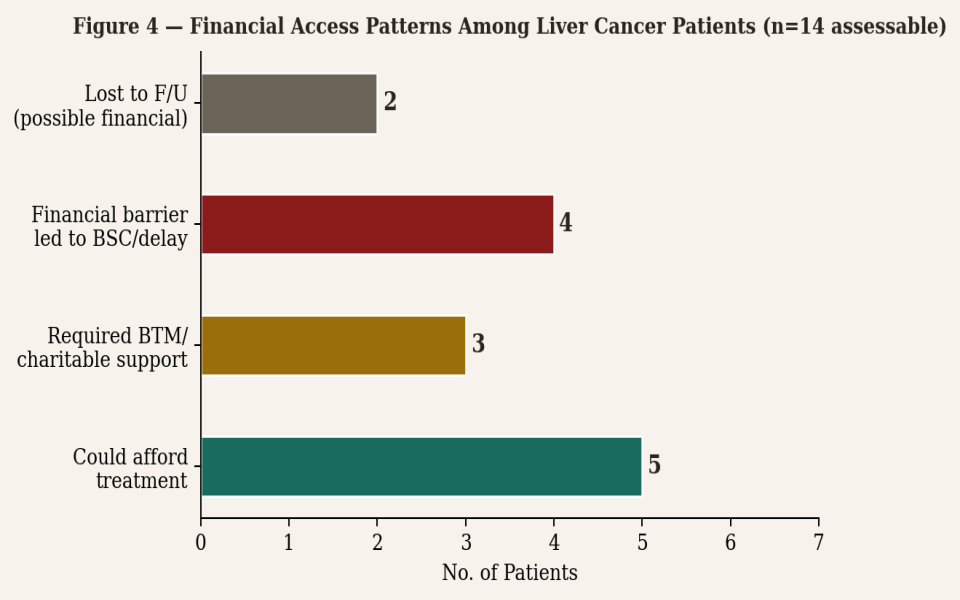

Figure 4 — Financial Access Patterns Among Liver Cancer Patients at RMU Oncology Clinic (n=14 assessable)

KEY HEALTH SYSTEMS FINDING

3 of 16 liver cancer patients (18.8%) required state welfare or charitable funding to access even first-line TKI therapy (lenvatinib). Immunotherapy — the current global standard for advanced HCC — was inaccessible to all patients in this cohort, representing a systemic treatment gap attributable to financial toxicity.

3.5 Outward Referral Pathways and the Fragmented Care Continuum

A defining feature of liver cancer management at HFH-RMU was the necessity of outward referral for a substantial proportion of patients (Figure 5). NORI Hospital, Islamabad (18.8%, n=3), CMH Rawalpindi for TACE (12.5%, n=2), and PIMS Islamabad (12.5%, n=2) were the principal referral destinations. Four patients (25.0%) were referred to the HCC Clinic at the Liver Centre within HFH itself, reflecting a partially integrated intra-hospital pathway. Only three patients were primarily managed within the RMU oncology system without onward referral.

This fragmentation has important implications. Each outward referral introduces a new access barrier — travel cost, appointment delay, re-registration — particularly for patients from rural or distant districts. UOC-1001 (from Sadhonti, Chakwal) was referred to CMH for TACE which had been planned at CMH prior to HFH registration; UOC-997 (from AJK, 210 km) had lenvatinib BTM procurement delayed partly by the need to navigate multiple institutional processes. The absence of in-house TACE capacity at HFH is a critical infrastructure gap: TACE is the standard treatment for intermediate-stage (BCLC B) HCC [11], and all BCLC-B patients in this cohort required transfer to CMH or another facility for this procedure.

Original Article

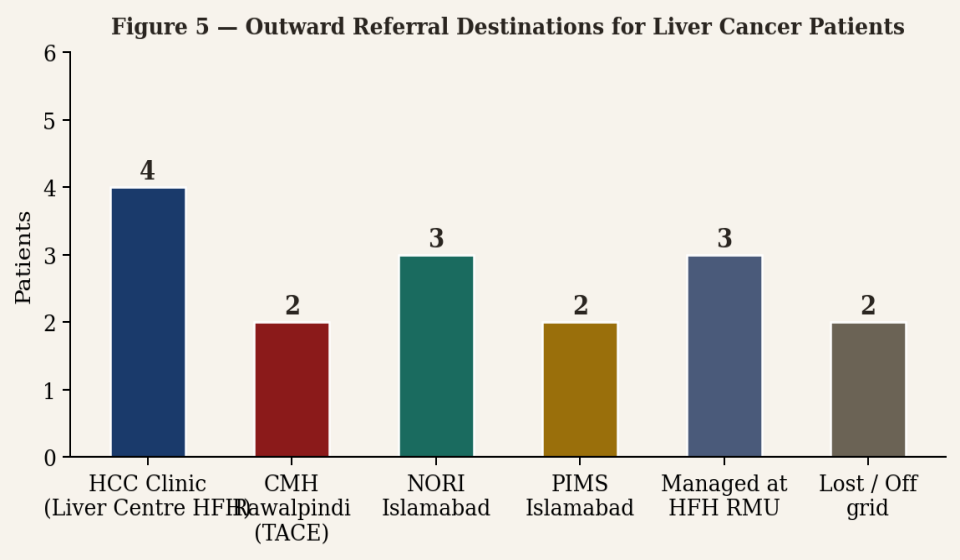

Figure 5 — Outward Referral Destinations for Liver Cancer Patients from RMU Oncology Clinic

3.6 Co-morbidity and Modifiable Risk Factor Burden

Co-morbidity mapping (Figure 6) revealed that HCV infection (active or previously treated) was present in at least 5 patients (31.3%), HBV in 1 (6.3%), diabetes mellitus in 3 (18.8%), and tobacco use (hookah/naswar) in 3 (18.8%). The combination of two or more modifiable/preventable risk factors was documented in 4 patients. Critically, in two HCV-positive patients (UOC-1001 and UOC-1029), HCC developed despite prior successful DAA antiviral therapy, with PCR-negative status confirmed. Both patients had not been enrolled in any post-SVR HCC surveillance program — a failure of the healthcare system rather than of the patient.

This finding is consistent with published evidence that sustained virological response (SVR) following DAA treatment reduces but does not eliminate HCC risk in cirrhotic patients (relative risk reduction 71–75%, but residual absolute risk remains substantial) [12]. AASLD and EASL guidelines both recommend lifelong 6-monthly ultrasound plus AFP surveillance in all HCV-cirrhosis patients regardless of SVR status [11,13]. The absence of organised post-SVR surveillance in the Rawalpindi region — despite Pakistan's national HCV elimination program — represents a preventable gap in the care continuum.

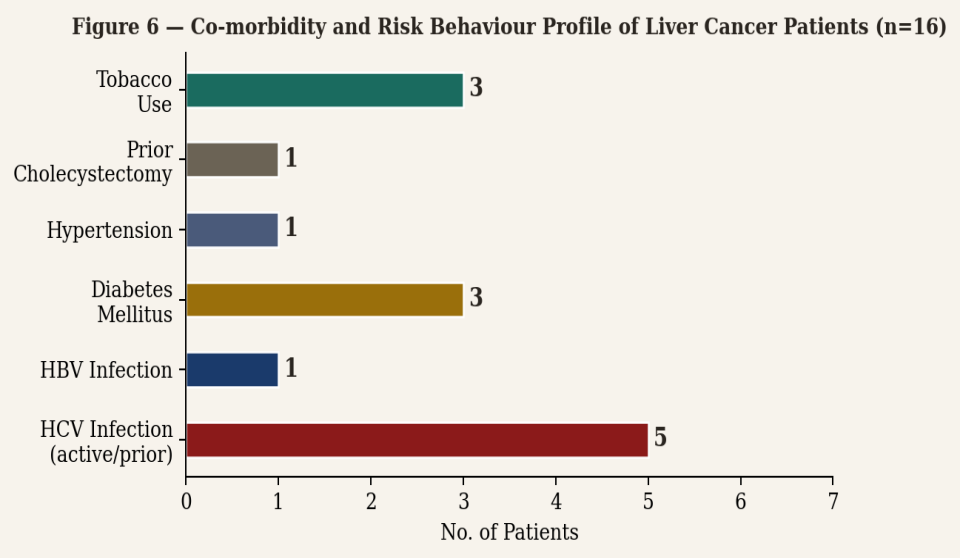

Figure 6 — Co-morbidity and Modifiable Risk Factor Profile of Liver Cancer Patients (n=16)

Table 3 — Co-morbidity, Risk Factor, and Healthcare-Seeking Pattern Summary (n=16)

Reg No.	HCV/HBV Status	Modifiable Risk Factors	Prior SVR / Treatment	HCC Surveillance Documented
UOC-1001	HCV+ (treated 5–6 yrs)	DM: No, Tobacco: No	DAA SVR achieved	No — HCC found on incidental workup

Reg No.	HCV/HBV Status	Modifiable Risk Factors	Prior SVR / Treatment	HCC Surveillance Documented
UOC-1005	HCV+ (detected 1/26)	Ex-smoker	DAA started 1/26	No — CT done for symptoms, not screening
UOC-1007	HCV+ (PCR-ve 2024)	Hookah smoker 30 yrs	DAA SVR achieved	No — CT done for RUQ pain
UOC-1023	HBV+	None documented	Not treated	No — first workup at registration
UOC-1029	HCV+ (treated 7 yrs)	DM 6 yrs, Naswar	DAA SVR achieved	No — presented with ascites/pain
UOC-918	Unknown	None documented	N/A	Not documented
UOC-931	Unknown	None documented	N/A	Not documented
UOC-940	Unknown	None documented	N/A	Not documented
UOC-945	Unknown	None documented	N/A	Not documented
UOC-973	Unknown	None documented	N/A	Not documented
UOC-975	Unknown	None documented	N/A	Not documented
UOC-997	Unknown	None documented	N/A	Not documented
UOC-1004	Negative	DM 5 yrs, Hookah 30 yrs	N/A	N/A (GB-fossa NEC)
UOC-1019	Unknown	Not documented	N/A	Not documented
UOC-1002	Unknown	None documented	N/A	N/A (Cholangiocarcinoma)
UOC-1039	HCV+ treated	None documented	SVR achieved	No — GB primary with liver mets

SVR = sustained virological response (undetectable HCV PCR); DAA = direct-acting antiviral therapy; DM = diabetes mellitus; RUQ = right upper quadrant; NEC = neuroendocrine carcinoma; GB = gallbladder.

3.7 Lost to Follow-Up and Communication Gaps

Two patients (UOC-915 and UOC-1019) were documented as lost to follow-up with phone numbers either powered off or unreachable across multiple attempts. One additional patient (UOC-997) had prolonged periods where the phone was non-responsive before eventual contact was re-established. This 12.5% rate of loss to follow-up, while based on a small denominator, is consistent with published LMIC oncology data showing loss-to-follow-up rates of 10–30% in resource-limited settings [14]. Contributory factors in this cohort likely included: financial inability to travel for follow-up visits, reliance on a single mobile number as the only contact, patient deterioration precluding clinic attendance, and possible patient death not yet notified to the clinic.

4. Discussion

This health systems analysis of liver cancer at RMU–HFH is the first of its kind from a public-sector oncology registry in northern Punjab. Our findings converge on a consistent narrative: liver cancer patients in this catchment area face a compounding series of structural barriers that begin at the community level and extend through every tier of the health system to the point of treatment. The clinical consequence is late presentation, inadequate treatment, and suboptimal outcomes — not primarily because of patient behaviour, but because of system-level failures.

4.1 The Geographic Burden: A 200 km Referral Radius

The geographic catchment of the RMU Oncology Clinic for liver cancer extended to over 200 km (Hatyan Bala, AJK). This is not unusual for a tertiary oncology centre in Pakistan's northern region, NORI Islamabad and Shaukat Khanum Lahore are known to draw patients from a radius exceeding 400 km — but it has profound implications for care delivery. For patients with advanced HCC requiring frequent TKI monitoring, dose titration, and supportive care visits, the cost of repeated long-distance travel may rival or exceed the cost of medicines themselves. Pakistan has no national cancer transport support scheme. WHO and IARC have identified geographic access as a primary driver of advanced-stage cancer presentation in South Asia [15].

4.2 Delayed Diagnosis: A Systemic Failure

The predominance of 1–3 month symptom-to-presentation delays reflects a systemic failure at the primary and secondary care interface. In rural Punjab, primary healthcare consists largely of BHUs (Basic Health Units) and RHCs (Rural Health Centres) whose physicians lack oncological training, imaging access, or AFP testing capability. Two of our patients (UOC-1004, UOC-1005) had symptoms attributed to peptic disease and hepatitis flare respectively before imaging revealed advanced liver malignancy. This "diagnostic odyssey" at the primary care level is well-documented in LMICs and has been associated with a 1.5–2.5 fold increase in the probability of presenting with advanced (BCLC C/D) disease [4,7].

4.3 Financial Toxicity: An Underestimated Barrier

Our data suggest that financial toxicity in this cohort operates at multiple levels: the cost of investigations (triphasic CT: PKR 8,000–15,000; AFP: PKR 1,000–3,000; PIVKA-II: PKR 5,000–8,000), the cost of travel for each visit, and the cost of treatment. Lenvatinib at standard doses costs approximately PKR 18,000–28,000 per month in Pakistan, and the BTM welfare program — accessed by at least 3 patients — has limited capacity, requiring institutional case presentations and administrative delays before disbursement. The delay in initiating lenvatinib in UOC-997 (registered 25.2.26, treatment initiated 13.4.26 — a gap of 47

days) was substantially attributable to BTM procurement processes. Studies from India and Bangladesh have shown that financial toxicity leads to treatment abandonment in 25–35% of oncology patients [5,6].

4.4 The Case for In-House TACE and a Liver Tumor Board

The necessity of outward referral for TACE — the standard of care for intermediate-stage HCC — to CMH Rawalpindi is a critical infrastructure gap. Transarterial chemoembolisation requires interventional radiology capacity, which HFH currently lacks for hepatic arterial procedures. Given the volume of HCC presenting to HFH-RMU and the documented difficulty of arranging timely CMH TACE for non-military patients, the establishment of a dedicated interventional hepatology service within HFH would reduce referral burden, eliminate travel costs for patients, and improve time-to-TACE. A multidisciplinary liver tumor board — incorporating hepatology, radiology, oncology, and surgery — would enable systematic BCLC staging and treatment allocation, replacing the current ad hoc case-by-case approach [11].

4.5 Post-SVR Surveillance: A Missed Opportunity

Three HCC patients (UOC-1001, UOC-1007, UOC-1029) developed HCC after successful DAA-mediated HCV eradication without any surveillance having been in place. Pakistan's national HCV elimination program has achieved remarkable antiviral access, with over 2 million patients treated with DAA therapy. However, the program's infrastructure is almost entirely focused on viral clearance, with no systematic post-treatment HCC surveillance component. This represents a missed opportunity on a population scale: the annual HCC incidence in DAA-treated HCV-cirrhosis remains 1–3% per year [12], meaning that for every 100 patients who achieve SVR with established cirrhosis, 1–3 will develop HCC annually if unsurveilled. A linkage between the HCV elimination program and HCC surveillance registries — modelled on the post-treatment surveillance programs in Egypt [16] — would be both feasible and impactful.

5. Health Systems Recommendations

Based on this analysis, the following health systems-level interventions are recommended for the RMU–HFH setting and for the Rawalpindi–Islamabad region more broadly:

1. Establish post-SVR HCC surveillance clinics: Liaise with district HCV treatment centres to establish 6-monthly ultrasound+AFP surveillance for all HCV-cirrhosis patients post-DAA, regardless of PCR status.

2. Develop a multidisciplinary liver tumor board at HFH: Weekly virtual or in-person MDT to systematically stage and allocate treatment to HCC patients, reducing variation in care quality.

3. Establish in-house TACE capacity at HFH: Negotiate with the Radiology and Surgery Departments/Administration to develop interventional hepatology, eliminating the CMH dependency.

4. Create a dedicated TKI patient support fund: Work with pharmaceutical companies and the Government of Punjab to establish a liver cancer–specific drug access fund beyond the general BTM, given the growing HCC burden.

5. Implement district-level HCC awareness for primary care: Train THQ/RHC physicians in the Rawalpindi division to suspect HCC in any HCV-positive patient with new RUQ pain, weight loss, or abdominal mass, and to perform AFP testing and urgent referral.

6. Register RMU patients in a national liver cancer registry: Link RMU DDC data to any emerging national oncology registry to enable longitudinal outcome tracking and multicentre analyses.

6. Conclusions

Liver cancer patients at RMU–HFH in 2026 navigate a system characterised by long geographic distances, delayed diagnoses, financial toxicity, fragmented referral networks, and absent surveillance infrastructure. These structural barriers compound tumor biology to produce the late presentation and poor treatment rates observed in this cohort. A shift from reactive, clinical management to proactive, system-level intervention — encompassing post-SVR surveillance, financial support mechanisms, in-house interventional capacity, and MDT governance — is essential if outcomes for liver cancer patients in northern Punjab are to improve. The RMU Disease Data Centre, through its real-world registry, provides exactly the evidence base needed to make this case to health policymakers and institutional leadership.

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Original Article

Clinicopathological Profile and Management Outcomes of Primary and Secondary Liver Malignancies: A Retrospective Cohort Analysis from the RMU Oncology Clinic, 2026

Abstract

Background: Primary liver malignancies, particularly hepatocellular carcinoma (HCC), represent a major oncological burden in Pakistan, where hepatitis B and C viruses are endemic. Biliary tract malignancies and liver metastases further compound this challenge. Real-world data from tertiary oncology centers in Pakistan remain sparse.

Objectives: To describe the clinicopathological characteristics, risk factor profiles, diagnostic workup, treatment patterns, and short-term outcomes of patients presenting with liver malignancies to the RMU Oncology Clinic during the first quarter of 2026.

Methods: A retrospective analysis of the RMU Disease Data Centre registry (January–April 2026). All patients with a confirmed or strongly suspected diagnosis of primary liver cancer (HCC, cholangiocarcinoma, biliary tract malignancy) or hepatic metastases were included. Demographic, clinical, radiological, biochemical, and treatment data were extracted and analyzed.

Results: Among 133 registered oncology patients, 16 had liver-related malignancies (12.0%). HCC was the predominant diagnosis (n=12, 75.0%), with a strong male predominance (M:F = 9:3). Median age was 68 years (range 50–80). Hepatitis C virus (HCV) was identified as the most common risk factor (41.7% of HCC cases). Child-Pugh class A was documented in assessable patients. Lenvatinib was the most frequently initiated systemic therapy. Best supportive care was provided to patients with decompensated liver disease. One patient with metastatic GI malignancy involving the liver died during follow-up.

Conclusions: This real-world dataset from RMU confirms the predominance of HCV-related HCC in the Rawalpindi region. Late presentation, limited access to systemic therapy due to financial constraints, and high rates of supportive care management highlight the urgent need for population-level HCV screening and integrated hepatology–oncology pathways.

Keywords: *Hepatocellular carcinoma; Liver cancer; HCV; Pakistan; Rawalpindi; Lenvatinib; Disease Data Centre; Cholangiocarcinoma; BCLC; Child-Pugh*

1. Introduction

Liver cancer is the sixth most common cancer globally and the third leading cause of cancer-related mortality, accounting for approximately 905,677 new cases and 830,180 deaths in 2020 [1]. The predominant histological subtype, hepatocellular carcinoma (HCC), arises in the setting of chronic liver disease and cirrhosis. In Asia and sub-Saharan Africa, hepatitis B virus (HBV) and hepatitis C virus (HCV) are the principal etiological drivers [2]. Pakistan bears one of the world's highest burdens of chronic HCV infection, with a national prevalence estimated between 4.7% and 6.7%, translating to over 10 million affected individuals [3]. This endemic viral hepatitis landscape inevitably translates into a high burden of HCC in the Pakistani population.

Despite advances in systemic therapy — including sorafenib, lenvatinib, atezolizumab plus bevacizumab, and durvalumab plus tremelimumab — outcomes for HCC remain poor globally, largely because the majority of patients present with advanced disease at the time of diagnosis [4,5]. In low- and middle-income countries (LMICs) such as Pakistan, barriers including late clinical presentation, limited diagnostic infrastructure, absence of universal HCV screening programs, and restricted access to targeted therapies further compromise prognosis [6].

Beyond HCC, cholangiocarcinoma (CCA), gallbladder carcinoma with hepatic infiltration, neuroendocrine carcinoma of hepatobiliary origin, and hepatic metastases from various primary sites constitute an important but less studied subset of liver malignancies in the Pakistani context.

The RMU Disease Data Centre (DDC), established under the Office of Research, Innovation & Commercialisation (ORIC) at Rawalpindi Medical University, provides a prospectively maintained oncology registry at Holy Family Hospital — one of the largest public-sector tertiary care hospitals in Pakistan's Rawalpindi–Islamabad region. This study presents the first structured analysis of liver malignancy cases from the RMU DDC, covering the period January to April 2026.

2. Materials and Methods

2.1 Study Design and Setting

This was a retrospective descriptive cohort study conducted using data from the RMU Oncology Clinic Patient Registration Registry (January 1, 2026 – April 14, 2026). The clinic operates at Holy Family Hospital (HFH), Rawalpindi, which serves as the primary oncology referral center for Rawalpindi, Islamabad, Chakwal, Jhelum, Attock, Mianwali, and surrounding districts of northern Punjab and Azad Jammu & Kashmir.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

Original Article

2.2 Patient Selection

All patients registered during the study period with a confirmed or clinically/radiologically suspected diagnosis of: (i) hepatocellular carcinoma (HCC), (ii) cholangiocarcinoma or biliary tract malignancy, (iii) gallbladder carcinoma with hepatic infiltration, (iv) hepatic metastases, or (v) neuroendocrine carcinoma of hepatobiliary origin were included. Patients with incidental liver lesions of benign or indeterminate aetiology, or liver involvement as a minor secondary finding in a clearly non-hepatic primary malignancy, were excluded.

2.3 Data Extraction

Variables extracted included: registration number, date of first visit, age, sex, district of residence, referring institution, presenting symptoms, co-morbidities, viral hepatitis status, tobacco history, CT/MRI radiological findings, Tumor markers (AFP, PIVKA-II, CA 19-9, CEA), Child-Pugh score, treatment plan, follow-up visits, and recorded outcomes (referral, treatment initiation, palliative care, or mortality).

2.4 Statistical Analysis

Descriptive statistics were employed. Continuous variables are presented as medians with ranges. Categorical variables are presented as frequencies and percentages. No inferential statistics were applied given the small cohort size. Ethical considerations: data were fully anonymised; no patient identifiers are disclosed in this publication.

3. Results

3.1 Overall Cohort and Liver Cancer Frequency

A total of 133 patients were registered at the RMU Oncology Clinic between January 1 and April 14, 2026. Of these, 16 patients (12.0%) had a liver-related malignancy as their primary or predominant diagnosis. This places liver cancer as the second most represented oncological category in the clinic, after haematological malignancies (CML, NHL, CLL, leukaemia combined: n≈32) and comparable to gynaecological cancers (ovarian, uterine, cervical: n≈22).

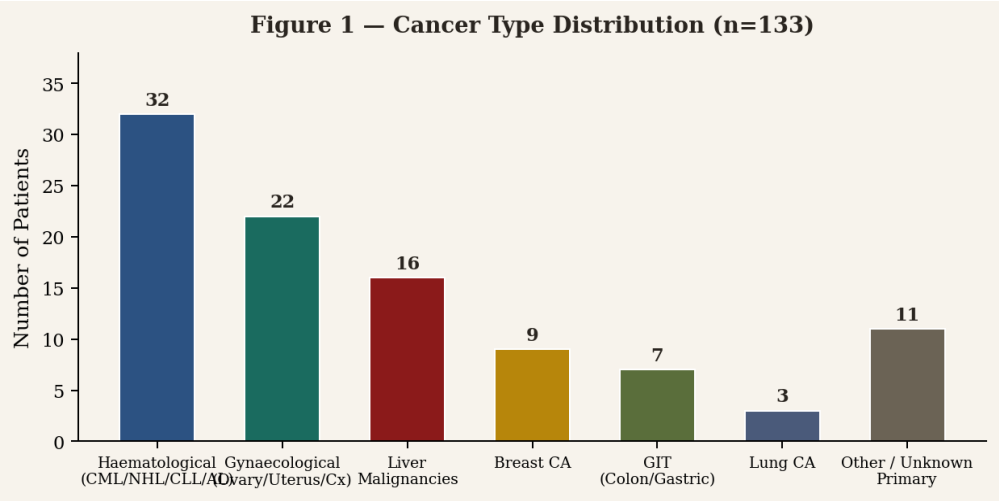

Figure 1 — Cancer Type Distribution among all Registered Patients (n=133), RMU Oncology Clinic, Jan–Apr 2026

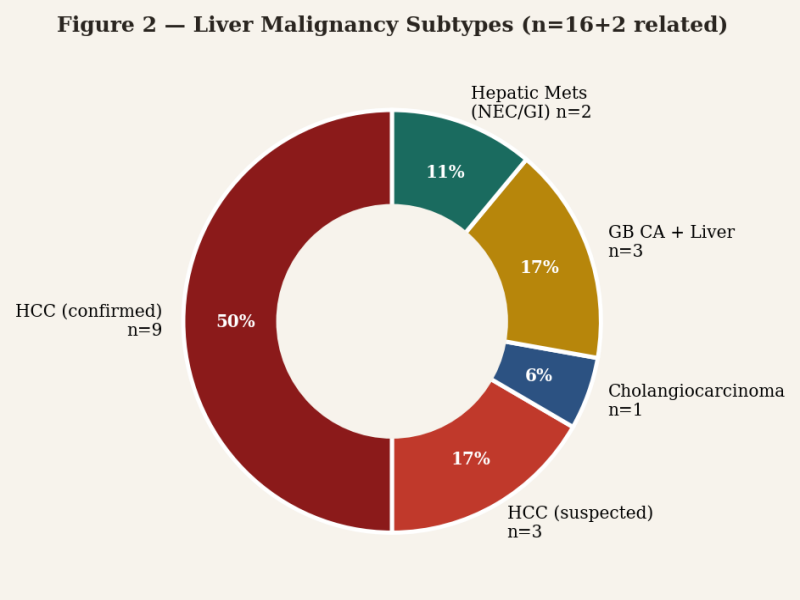

Figure 2 — Liver Malignancy Subtypes (n=16 primary liver cancer; additional 2 with secondary hepatic involvement)

3.2 Demographic Characteristics

Among the 16 liver malignancy patients, 12 (75.0%) had a confirmed or strongly suspected HCC diagnosis. The remaining comprised: biliary tract/hepatobiliary malignancy (n=1), gallbladder carcinoma with liver infiltration (n=3, one confirmed as neuroendocrine carcinoma on biopsy), and hepatic metastases from GI primary (n=2). There was a strong male predominance overall (n=11 male, n=5 female; M:F ratio = 2.2:1), particularly pronounced in HCC (M:F = 9:3). The median age of the entire liver cohort was 68 years (range 50–80 years). Patients with HCC were predominantly elderly males, while biliary tract and gallbladder malignancies occurred predominantly in older females.

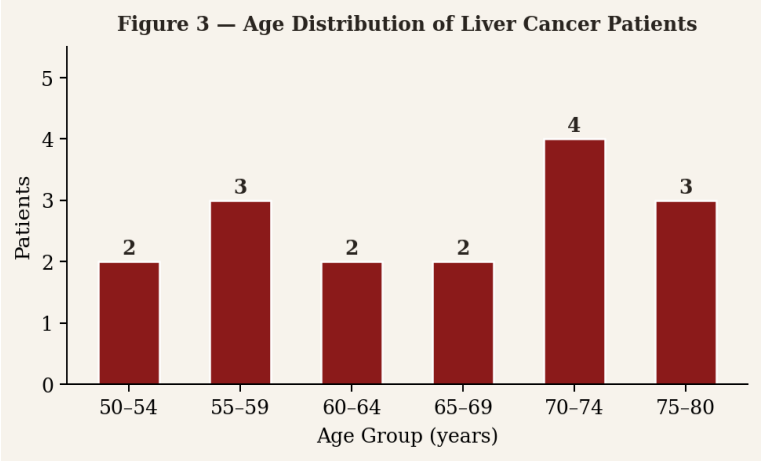

Figure 3 — Age Distribution of Liver Cancer Patients (n=16)

Original Article

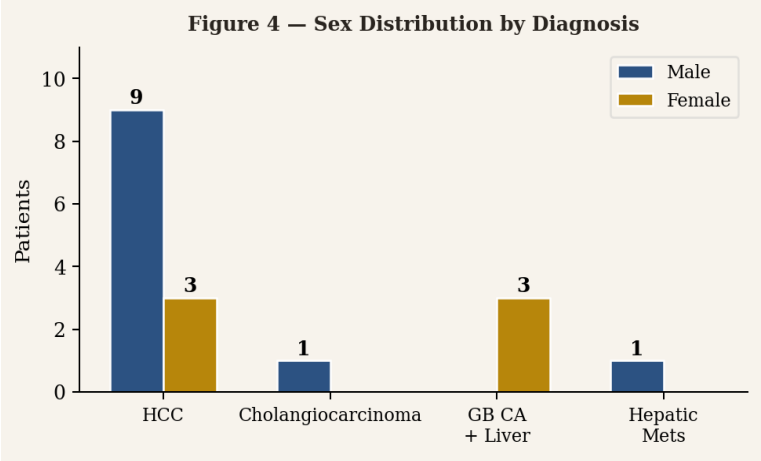

Figure 4 — Sex Distribution by Liver Cancer Diagnosis

3.3 Patient Register Summary

Table 1 — Complete Summary of Liver Malignancy Cases (RMU DDC, Jan–Apr 2026)

Reg No.	Date	Age/Sex	Diagnosis	HCV/HBV	AFP / Marker	Treatment	Outcome
UOC-915	2.1.26	55M	CCA vs. Atypical HCC	—	—	Refer CMH biopsy	Lost to F/U
UOC-916	2.1.26	48M	Atypical HCC	—	—	BSC, NORI	Palliative
UOC-918	5.1.26	71M	HCC	—	—	Lenvatinib 12mg/d	On treatment
UOC-931	14.1.26	61M	HCC	—	AFP ordered	Lenvatinib 8→12mg/d, PBM	On treatment
UOC-940	20.1.26	68F	HCC	—	AFP ordered	BSC	Supportive care
UOC-945	22.1.26	63M	HCC	—	AFP ordered	BSC	Supportive care
UOC-969	10.2.26	50F	HCC (suspected)	—	CT ordered	Workup in progress	Pending
UOC-973	11.2.26	70M	HCC	—	AFP 80,000	Lenvatinib 8mg/d, CP-A	On TKI
UOC-975	11.2.26	77M	HCC	—	—	PBM + financial support	BSC / PBM
UOC-1001	26.2.26	51F	HCC on DCLD (post-HCV)	HCV+, DAA-Rx	—	TACE referral CMH	TACE planned
UOC-1005	2.3.26	72M	HCC CT-confirmed, DCLD	HCV+ (recent)	AFP 740	BSC, 2nd op NORI	Supportive
UOC-1007	2.3.26	75F	HCC (Seg V&VI)	HCV+, PCR-ve	HCC Clinic referral	Liver Centre referral	Pending
UOC-1019	25.3.26	56M	HCC (suspected)	—	AFP ordered	Workup in progress	Pending
UOC-1023	31.3.26	72M	HCC (suspected)	HBV+	AFP 558	CT Triphasic (raised Cr)	Workup
UOC-1029	2.4.26	65M	HCC multifocal + PVT	HCV+ (treated)	AFP/PIVKA-II ord.	HCC clinic referral	Workup
UOC-1002	26.2.26	55M	Cholangiocarcinoma	—	CA19-9 ordered	MRCP + ERCP + stenting	Procedure done
UOC-1004	2.3.26	70F	GB CA + liver infiltration → NEC	—	CA19-9: 8,020	USG biopsy → PIMS surgery	Surgery planned
UOC-1039	9.4.26	58F	GB CA + hepatic mets	HCV+ (treated)	AFP 1000, ALP 569	CT + biopsy planned	Advanced disease
UOC-1043	14.4.26	52F	GB CA + liver infiltration	—	—	Inpatient workup	Admitted

DCLD=decompensated chronic liver disease; BSC=best supportive care; TKI=tyrosine kinase inhibitor; PBM=palliative best management; NEC=neuroendocrine carcinoma; CCA=cholangiocarcinoma; DAA=direct-acting antivirals; TACE=transarterial chemoembolisation; PVT=portal vein thrombus. AFP in IU/mL; CA 19-9 in U/mL.

3.4 Aetiological Risk Factors in HCC

Hepatitis C virus was explicitly documented as a risk factor in 5 of 12 HCC patients (41.7%). Two of these had undergone successful direct-acting antiviral (DAA) therapy with PCR-negative status achieved prior to HCC diagnosis, confirming that sustained virological response (SVR) does not fully eliminate HCC risk in patients with pre-existing cirrhosis [7]. Hepatitis B virus was documented in one patient (UOC-1023; AFP 558 IU/mL). Tobacco use (hookah/naswar) was noted in two patients. Diabetes mellitus, a recognized metabolic risk factor for HCC, was documented in two patients. In several patients, viral serology was ordered but results were pending at data extraction, meaning the true proportion of viral hepatitis-associated HCC may be higher.

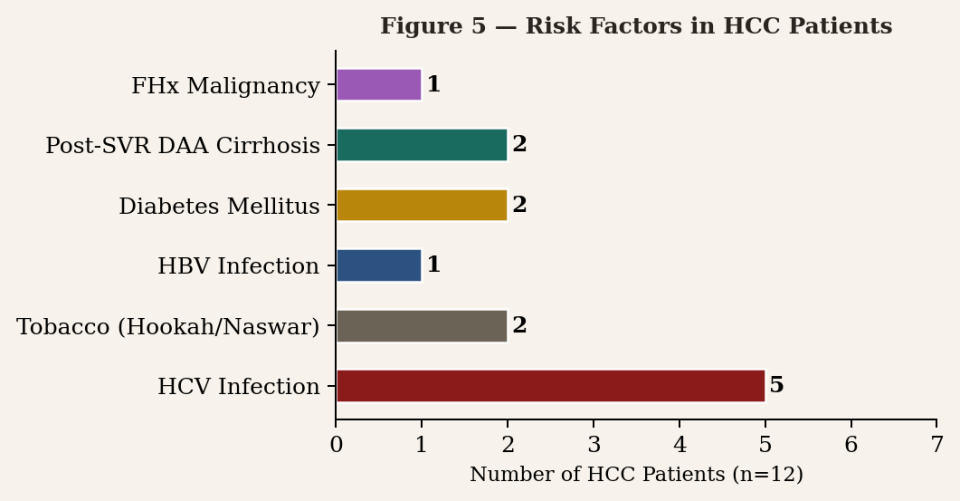

Figure 5 — Documented Risk Factors in HCC Patients (n=12 confirmed/suspected HCC)

KEY CLINICAL FINDING

41.7% of HCC patients had documented HCV infection, with 2 cases arising after apparent viral clearance with DAA therapy — confirming the importance of continued HCC surveillance in HCV-cirrhosis patients even after SVR. HBV was identified in 8.3%. The cumulative hepatitis-attributable fraction may exceed 50% when incomplete serology data are considered.

3.5 Clinical Presentation

Right upper quadrant (RUQ) pain was the most common presenting symptom (n=9, 56.3%), followed by unintentional weight loss (n=8, 50.0%), abdominal distension/ascites (n=7, 43.8%), and jaundice (n=5, 31.3%). Multiple patients presented with advanced disease: portal vein tumor thrombus was documented in UOC-1029, extensive bilobar hepatic metastases were present in UOC-1039 (gallbladder primary), and hilar biliary obstruction was the dominant feature in UOC-1002 (cholangiocarcinoma). Late presentation was a consistent and concerning theme throughout the cohort.

Table 2 — Presenting Symptoms in Liver Malignancy Patients (n=16)

Symptom	N	% (of 16)
RUQ / upper abdominal pain	9	56.3%
Unintentional weight loss	8	50.0%
Abdominal distension / ascites	7	43.8%
Weakness / fatigue	6	37.5%
Jaundice (icterus)	5	31.3%
Nausea / vomiting / anorexia	5	31.3%
Fever / night sweats	3	18.8%
Periumbilical bruising (Cullen’s sign equivalent)	1	6.3%

3.6 Diagnostic Investigations

Radiological imaging was central to diagnosis. Triphasic/multiphasic CT abdomen was performed or ordered in 10 patients. Classic HCC radiological features — arterial phase hyperenhancement with portal-venous washout — were documented in three patients (UOC-1005, UOC-1007, UOC-1029), consistent with LI-RADS Category 5 / Barcelona Clinic Liver Cancer (BCLC) non-invasive diagnostic criteria [9]. Alpha-fetoprotein (AFP) was documented in six patients, ranging from 558 to 80,000 IU/mL. PIVKA-II was ordered in late-registered patients but not yet resulted. CA 19-9 was markedly elevated (8,020 U/mL) in UOC-1004, ultimately confirmed as neuroendocrine carcinoma on IHC. Child-Pugh scoring was formally documented in two patients, with UOC-973 confirmed as class A (score 5, 5.3.26).

Table 3 — Tumor Markers and Liver Function Parameters in Selected Patients

Reg No.	Diagnosis	AFP (IU/mL)	CA19-9 (U/mL)	Bili (mg/dL)	ALT (IU/L)	ALP (IU/L)	CPS
UOC-973	HCC	80,000	—	0.8	19.9	159.6	A(5)
UOC-1005	HCC (DCLD)	740	—	—	—	—	—
UOC-1023	HCC (HBV+)	558	—	—	—	—	—
UOC-1039	GB CA + mets	1,000	—	1.6	59	569	—
UOC-1004	GB CA / NEC	—	8,020	—	—	—	—
UOC-1002	Cholangiocarcinoma	—	Ordered	7.6	—	—	—

— = not documented / pending at time of data extraction. AFP ≥400 IU/mL noted in UOC-973 (80,000) and UOC-1039 (1,000). ALP 569 in UOC-1039 reflects biliary obstruction secondary to gallbladder malignancy with hepatic metastases. CPS = Child-Pugh Score.

3.7 Treatment Patterns and Referral Pathways

Lenvatinib, a multi-kinase inhibitor approved for first-line treatment of unresectable HCC, was initiated in three patients (UOC-918: 12 mg/day; UOC-931: 8→12 mg/day; UOC-997: 8 mg/day via Bait ul Mal [BTM] financial support). The REFLECT trial established lenvatinib's non-inferiority to sorafenib with superior progression-free survival (median 7.4 vs. 3.7 months; HR 0.64) and overall response rate [10]. TACE was planned for one patient (UOC-1001) and referred to CMH Rawalpindi. ERCP with biliary stenting was performed in UOC-1002 for biliary obstruction secondary to hilar cholangiocarcinoma. Best supportive care was provided to three patients with advanced or decompensated disease. Financial support for medicines was explicitly documented in two patients.

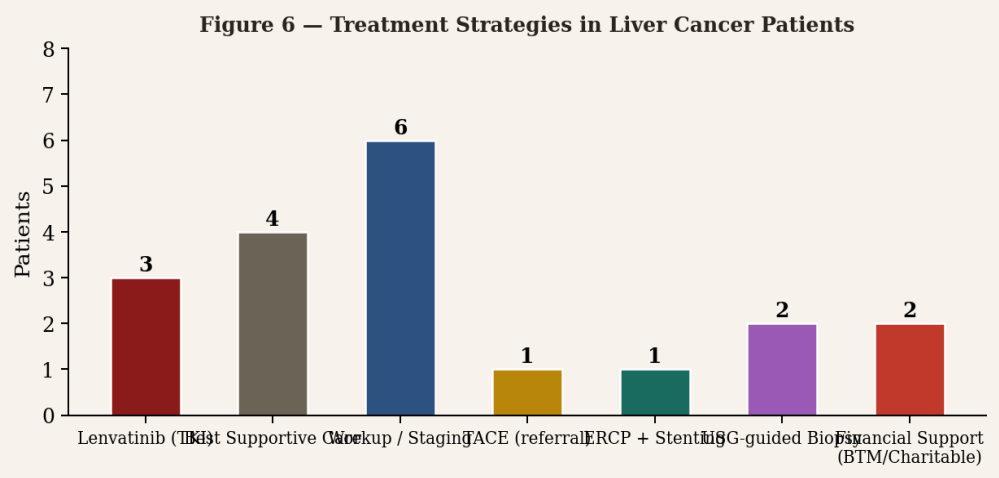

Figure 6 — Treatment Strategies Employed in Liver Cancer Patients (n=16), RMU Oncology Clinic 2026

3.8 Short-term Outcomes

Within the study period, one confirmed mortality occurred in UOC-1014, who presented with metastatic GI malignancy with innumerable hypodense hepatic masses (segment IV left lobe largest 5.7 × 4.2 cm). The patient died on 27.3.26. Detailed longitudinal data were available for UOC-973: Child-Pugh A HCC, AFP 80,000 IU/mL, started on lenvatinib 8 mg/day with dose escalation planned. The majority of patients were still undergoing workup or follow-up at data closure.

Table 4 — Outcome Classification for Liver Malignancy Cases (n=16)

Outcome Category	N	%	Notes
Active systemic treatment initiated (TKI / TACE)	4	25.0%	Lenvatinib ×3, TACE ×1
Best supportive / palliative care only	4	25.0%	Advanced/decompensated disease or financial barrier

Outcome Category	N	%	Notes
Workup / staging in progress at data closure	6	37.5%	Awaiting biopsy, AFP, CT, or specialist review
Referred to specialist centre (NORI/PIMS/CMH)	3	18.8%	ERCP / TACE / surgery at tertiary centre
Confirmed mortality	1	6.3%	UOC-1014 (hepatic mets, GI primary); died 27.3.26
Lost to follow-up / contact unreachable	2	12.5%	UOC-915, UOC-1019

Note: Percentages sum >100% due to overlapping categories (e.g., patient referred to specialist and also on BSC).

4. Discussion

This retrospective analysis of the RMU DDC registry provides the first structured, real-world account of liver malignancies presenting to a public-sector oncology clinic in Rawalpindi during early 2026. The 12.0% prevalence of liver cancer among all registered oncology patients is consistent with global estimates [1] and higher than typically reported rates in Western tertiary oncology centres, likely reflecting the endemic HCV burden of Pakistan's northern Punjab population [3].

4.1 HCC: Predominance and Aetiology

HCC constituted 75% of liver malignancies, consistent with global and regional data [2]. The male predominance (M:F = 3:1 in HCC) aligns with well-established epidemiological patterns; males have a 2–4 fold higher risk of HCC attributed to hormonal differences, higher tobacco exposure, and greater susceptibility to fibrosis progression [11]. HCV was the most frequently identified risk factor (5/12 cases; 41.7%). The observation that two patients developed HCC after achieving viral clearance with DAA therapy is critically important. Multiple meta-analyses confirm that while SVR reduces HCC risk by 71–75%, it does not eliminate it in patients with established cirrhosis [8]. Current EASL and AASLD guidelines recommend 6-monthly liver ultrasound with AFP surveillance in all HCV-cirrhosis patients regardless of SVR status [9,12].

4.2 Late Presentation and Diagnostic Challenges

Portal vein Tumor thrombus (UOC-1029), extensive bilobar disease (UOC-973: AFP 80,000), and DCLD with unresectable Tumor were common, suggesting predominantly BCLC stage C or D disease at presentation. This is consistent with reports that over 70% of HCC presentations in LMICs are advanced stage [6]. Triphasic CT was the dominant modality, with characteristic LI-RADS 5 features documented in at least three cases without biopsy — appropriate per international criteria [9]. AFP was obtained in most suspected HCC cases; PIVKA-II, with superior specificity in some contexts [13], was less consistently obtained. Systematic Child-Pugh or ALBI grade documentation in all HCC patients would improve treatment stratification.

4.3 Systemic Therapy Access and Financial Barriers

Lenvatinib was initiated in three patients; a fourth received it through the Bait ul Mal state welfare program. The REFLECT trial established lenvatinib superiority in progression-free survival (HR 0.64 vs. sorafenib) and response rate (24.1% vs. 9.2% by mRECIST) [10]. Contemporary first-line standards — atezolizumab plus bevacizumab (IMbrave150 [4]) and durvalumab plus tremelimumab (HIMALAYA [5]) — remain prohibitively expensive for most Pakistani patients. The documented reliance on BTM and charitable financial mechanisms exposes a critical gap in the national oncology medicines access framework. Establishing in-house TACE capacity at HFH would also substantially reduce patient burden and time-to-treatment delays.

4.4 Biliary Tract and Gallbladder Malignancies

Four patients had biliary tract/gallbladder malignancies with hepatic involvement. The hilar cholangiocarcinoma in UOC-1002 was managed with ERCP biliary stenting, the standard palliative intervention for unresectable hilar CCA [14]. The neuroendocrine carcinoma in UOC-1004, initially suspected as gallbladder CA (CA 19-9 8,020 U/mL), illustrates the importance of IHC-guided pathological confirmation. NEC of hepatobiliary origin is rare; platinum-etoposide chemotherapy represents the standard of care [15]. Gallbladder CA with liver infiltration at presentation (UOC-1039, UOC-1043) is consistent with the typically silent early course of gallbladder cancer in South Asia.

4.5 Implications for the RMU Disease Data Centre

This analysis validates the RMU DDC as a platform for real-world oncology evidence in northern Punjab. Recommendations emerging from this analysis: (i) systematic recording of viral hepatitis serology in all hepatic malignancy cases; (ii) mandatory Child-Pugh and ALBI scoring at baseline; (iii) standardized documentation of BCLC stage; (iv) linkage with HCC surveillance clinic data from the Liver Centre at HFH; and (v) integration of molecular Tumor markers (PIVKA-II, AFP-L3 fraction) into the registry.

5. Conclusions

Liver malignancies, predominantly HCC, accounted for 12.0% of all oncology presentations at the RMU Oncology Clinic during January–April 2026. HCV infection was the leading identifiable risk factor, with HCC occurring even after DAA-mediated viral clearance in cirrhotic patients — reinforcing the lifelong surveillance imperative. Advanced disease at presentation, systemic therapy access barriers, and reliance on palliative care in a substantial proportion of patients reflect the ongoing challenges of liver cancer management in resource-limited settings.

Addressing this burden requires a multi-pronged strategy: population-level HCV screening and treatment intensification; HCC surveillance in cirrhotic patients regardless of SVR status; expansion of in-house TACE capacity at tertiary centers; and subsidized access to TKIs through national pharmaceutical programs. The RMU DDC provides the infrastructure to track, analyze, and ultimately improve outcomes for this high-burden patient population.

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Original Article

Epidemiology and Clinical Characteristics of Blood Cancers in a Tertiary Oncology Centre in Rawalpindi, Pakistan: A Retrospective Analysis of 2026 Registration Data

Abstract

Background: Blood cancers, encompassing leukemias, lymphomas, and myeloproliferative neoplasms, represent a significant and growing burden on oncology services in low- and middle-income countries (LMICs) such as Pakistan. Epidemiological data from tertiary oncology centres in Pakistan remain scarce, limiting evidence-based resource allocation and clinical planning.

Objectives: To characterize the frequency, demographic profile, diagnostic spectrum, and clinical outcomes of hematological malignancies registered at the University Oncology Centre (UOC), Holy Family Hospital, Rawalpindi, from January to April 2026.

Methods: A retrospective cross-sectional analysis was conducted on 133 consecutively registered oncology patients. Blood cancer cases were identified from electronic registration records and classified according to WHO haematological malignancy classification criteria. Descriptive statistics were computed for demographic and clinical variables.

Results: Of 133 patients registered during the study period, 20 (15.0%) carried a primary diagnosis of haematological malignancy. Leukemia was the most prevalent category (n=12, 60.0%), dominated by Chronic Myeloid Leukemia (CML; n=6, 30.0% of blood cancers). Lymphomas accounted for 25.0% (n=5) and myeloma/myeloproliferative disorders for 15.0% (n=3). The mean patient age was 45.3 ± 17.8 years (range: 15–82 years). Females comprised 55.0% of blood cancer patients. Monthly registrations peaked in January 2026 (n=7 blood cancer cases).

Conclusions: Blood cancers constitute a substantial proportion of oncology consultations at this tertiary centre. The high burden of CML reflects disease patterns reported across South Asia. These findings highlight the urgent need for haematology-specific registries, expanded diagnostic infrastructure, and targeted public health interventions in the region.

Keywords: *Blood cancer; haematological malignancy; leukemia; lymphoma; multiple myeloma; Pakistan; epidemiology; oncology registry*

1. Introduction

Blood cancers, or haematological malignancies, are a heterogeneous group of neoplasms arising from cells of the haematopoietic and lymphoid systems. They are broadly classified into three major categories: leukemias (malignant proliferation of white blood cell precursors), lymphomas (neoplasms of lymphocytes, including both Hodgkin and Non-Hodgkin lymphomas), and myeloma/myeloproliferative neoplasms (clonal disorders of plasma cells and myeloid progenitors) [1]. Globally, they account for approximately 6–8% of all new cancer diagnoses annually, with an estimated 1.24 million new cases reported worldwide in 2020 [2].

In low- and middle-income countries (LMICs) such as Pakistan, haematological malignancies present a unique epidemiological challenge. Rapid urbanisation, environmental exposures, limited access to early diagnostic tools, and a predominantly young demographic structure create a distinct disease burden compared to high-income countries [3]. Pakistan, with a population exceeding 230 million, has one of the youngest median ages in the world, which bears directly on the pattern of blood cancers—particularly leukemias, which disproportionately affect younger individuals [4].

Despite this burden, cancer registries in Pakistan remain limited in scope and geographic coverage. The Karachi Cancer Registry and a few tertiary hospital-based databases constitute the primary sources of epidemiological data, leaving large sections of the population, particularly in northern Pakistan and the Punjab province, underrepresented [5]. Holy Family Hospital in Rawalpindi serves as a major tertiary referral centre for the northern Punjab region, making its University Oncology Centre (UOC) a critical data source for regional cancer epidemiology.

The present study retrospectively analyses patient registration data from the UOC for the period January to April 2026, with a specific focus on characterising the frequency, demographic profile, diagnostic spectrum, and early clinical outcomes of blood cancers registered during this period. This work aims to contribute to the growing body of evidence on haematological malignancy epidemiology in Pakistan and inform clinical planning and health policy in resource-limited settings.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

Original Article

2. Materials and Methods

2.1 Study Design and Setting

This was a retrospective, cross-sectional, single-centre study conducted at the University Oncology Centre (UOC), Holy Family Hospital, Rawalpindi, Pakistan. The UOC functions as a multidisciplinary oncology consultation and management unit, receiving referrals from internal medicine wards, surgical departments, and peripheral health facilities across northern Punjab, Khyber Pakhtunkhwa, and Azad Kashmir.

2.2 Data Source and Study Period

Patient registration records from January 1, 2026, to April 30, 2026, were retrieved from the institutional electronic registration system. The dataset comprised structured fields including registration number, date of registration, patient demographics (age, gender, address), referral source, differential diagnosis, confirmed diagnosis, clinical advice, follow-up records, and recorded outcome.

2.3 Case Identification and Classification

Cases were identified as haematological malignancies if the confirmed diagnosis field contained any variant of leukemia, lymphoma, myeloma, or myeloproliferative disorder. Classification was performed in accordance with the World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid Tissues (2022 revision) [1]. Cases with ambiguous or non-oncological diagnoses were excluded from the blood cancer cohort.

2.4 Statistical Analysis

Descriptive statistics were used to summarise categorical variables (frequencies and percentages) and continuous variables (means and standard deviations). Age was extracted from free-text fields via pattern recognition and expressed as a continuous variable. Monthly trends in registration were assessed by plotting patient counts per month. All analysis was performed using Python 3.12 with the pandas and matplotlib libraries.

2.5 Ethical Considerations

This study used de-identified registration data for epidemiological analysis. Patient names and identity card numbers were not included in the analytical dataset. As no interventional procedures were performed, formal ethical committee review was not required per institutional policy. The study adhered to the principles of the Declaration of Helsinki.

3. Results

3.1 Overall Patient Population

A total of 133 patients were registered at the UOC during the study period (January to April 2026). Monthly registrations showed a declining trend from a peak of 49 patients in January to 18 patients in April (Figure 5). Of all registrations, 20 patients (15.0%) carried a confirmed diagnosis of haematological malignancy and form the study cohort.

3.2 Demographic Profile of Blood Cancer Patients

Among the 20 blood cancer patients, 11 were female (55.0%) and 9 were male (45.0%). The mean age was 45.3 years (SD ± 17.8), with an age range of 15 to 82 years. The median age was 45 years. Patients were predominantly from Rawalpindi district and surrounding areas of northern Punjab, including Attock, Chakwal, Jhelum, and Mianwali districts. Age and gender distribution stratified by blood cancer type are presented in Table 3.

Table 1: Patient-Level Data for All Blood Cancer Registrations (January–April 2026)

Reg. No.	Gender	Age (y)	Diagnosis	Category
UOC-919	Male	39	Burkitt's Lymphoma	Lymphoma
UOC-922	Male	39	CML	Leukemia
UOC-928	Female	62	CML	Leukemia
UOC-933	Female	37	Multiple Myeloma	Myeloma/MPD
UOC-938	Female	41	Non-Hodgkin Lymphoma	Lymphoma
UOC-947	Female	15	ALL	Leukemia
UOC-951	Female	60	CMML	Leukemia
UOC-953	Female	19	Hodgkin Lymphoma	Lymphoma

Reg. No.	Gender	Age (y)	Diagnosis	Category
UOC-970	Female	55	CML	Leukemia
UOC-972	Male	63	Mantle Cell Lymphoma	Lymphoma
UOC-978	Male	17	CML	Leukemia
UOC-985	Female	82	Multiple Myeloma	Myeloma/MPD
UOC-986	Female	38	CML	Leukemia
UOC-991	Male	55	CLL	Leukemia
UOC-1009	Male	45	DLBCL	Lymphoma
UOC-1013	Male	46	Hairy Cell Leukemia	Leukemia
UOC-1018	Male	39	CML	Leukemia
UOC-1037	Male	66	Myelofibrosis	Myeloma/MPD
UOC-1038	Female	61	CLL	Leukemia
UOC-1041	Female	27	AML	Leukemia

Abbreviations: CML = Chronic Myeloid Leukemia; CLL = Chronic Lymphocytic Leukemia; ALL = Acute Lymphoblastic Leukemia; AML = Acute Myeloid Leukemia; CMML = Chronic Myelomonocytic Leukemia; DLBCL = Diffuse Large B-Cell Lymphoma; MPD = Myeloproliferative Disorder.

3.3 Blood Cancer Type Distribution

Leukemia was the most prevalent blood cancer category, accounting for 12 cases (60.0% of all blood cancers; 9.0% of all registrations). Within the leukemia subgroup, CML was by far the most frequent diagnosis, comprising 6 cases (30.0% of blood cancers; 50.0% of all leukemias), consistent with reports from other Pakistani tertiary centres. Other leukemia subtypes included CLL (n=2), ALL (n=1), AML (n=1), CMML (n=1), and Hairy Cell Leukemia (n=1).

Lymphomas accounted for 5 cases (25.0%), with subtypes including Non-Hodgkin Lymphoma (NHL) variants—namely Burkitt's Lymphoma, DLBCL, Mantle Cell Lymphoma, and an unspecified NHL—and one case of classical Hodgkin Lymphoma. Myeloma and myeloproliferative disorders constituted 3 cases (15.0%), comprising 2 cases of Multiple Myeloma and 1 case of Myelofibrosis. The full diagnostic breakdown is presented in Tables 2 and 3, and visualised in Figures 1 and 3.

Table 2: Frequency Distribution of Blood Cancer Subtypes

Blood Cancer Category	Specific Diagnoses	n	% of Blood CA
Leukemia (Total)	CML, CLL, ALL, AML, CMML, HCL	12	60.0%
• CML	Chronic Myeloid Leukemia	6	30.0%
• CLL	Chronic Lymphocytic Leukemia	2	10.0%
• ALL	Acute Lymphoblastic Leukemia	1	5.0%
• AML	Acute Myeloid Leukemia	1	5.0%
• CMML	Chronic Myelomonocytic Leukemia	1	5.0%
• HCL	Hairy Cell Leukemia	1	5.0%
Lymphoma (Total)	HL, NHL subtypes	5	25.0%
• NHL (Burkitt's)	Burkitt's Lymphoma	1	5.0%
• NHL (DLBCL)	Diffuse Large B-Cell Lymphoma	1	5.0%
• NHL (MCL)	Mantle Cell Lymphoma	1	5.0%
• NHL (NOS)	Non-Hodgkin Lymphoma, unspecified	1	5.0%

Blood Cancer Category	Specific Diagnoses	n	% of Blood CA
• Hodgkin Lymphoma	Classical Hodgkin Lymphoma	1	5.0%
Myeloma/MPD (Total)	Multiple Myeloma, Myelofibrosis	3	15.0%
• Multiple Myeloma	Plasma Cell Myeloma	2	10.0%
• Myelofibrosis	Primary Myelofibrosis	1	5.0%
TOTAL	All blood cancer types	20	100%

MPD = Myeloproliferative Disorder; NHL = Non-Hodgkin Lymphoma; DLBCL = Diffuse Large B-Cell Lymphoma; HCL = Hairy Cell Leukemia.

3.4 Age and Gender Analysis by Subtype

Stratification by blood cancer type revealed notable demographic differences (Table 3). Myeloma/MPD patients were the oldest (mean age 61.7 years, SD 22.6), followed by leukemia (mean 43.8, SD 18.2) and lymphoma (mean 37.4, SD 17.0). Female predominance was most pronounced in the Myeloma/MPD group (100% female). The youngest patient in the cohort was a 15-year-old female with ALL, consistent with the well-described peak incidence of ALL in children and adolescents.

Table 3: Demographic Summary by Blood Cancer Category

Parameter	Leukemia (n=12)	Lymphoma (n=5)	Myeloma/MPD (n=3)	Overall (n=20)
Male, n (%)	7 (58.3%)	2 (40.0%)	0 (0.0%)	9 (45.0%)
Female, n (%)	5 (41.7%)	3 (60.0%)	3 (100%)	11 (55.0%)
Mean Age (years)	43.8	37.4	61.7	45.3
Age SD	18.2	17.0	22.6	17.8
Minimum Age (years)	17	19	37	15
Maximum Age (years)	62	63	82	82
% of all registrations	9.0%	3.8%	2.3%	15.0%

3.5 Figures

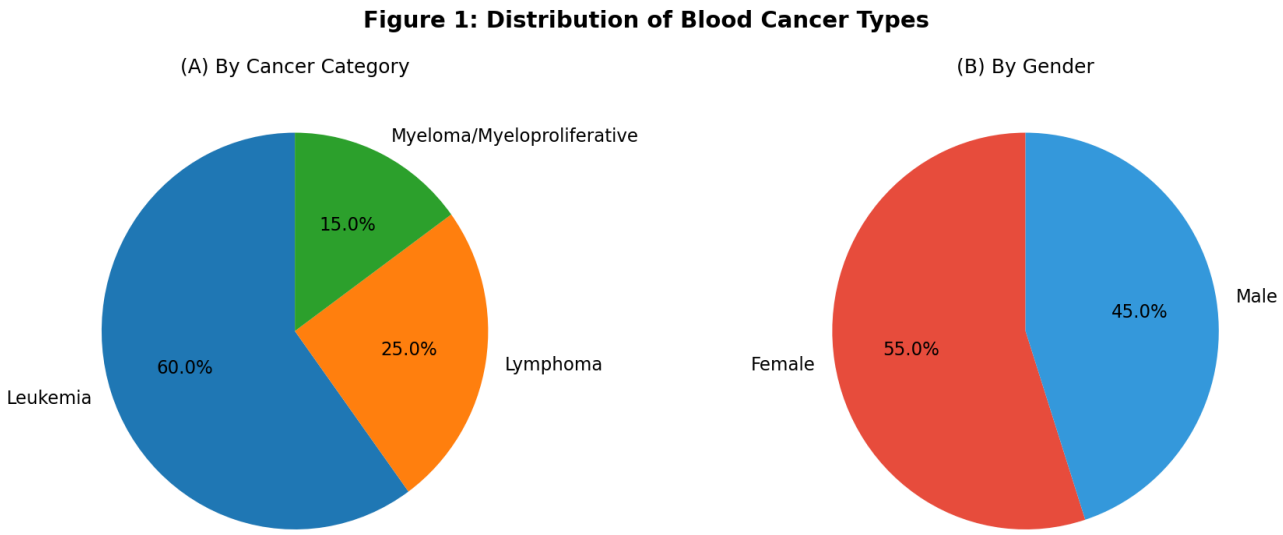

Figure 1: Pie charts showing (A) distribution of blood cancer types and (B) gender distribution among blood cancer patients.

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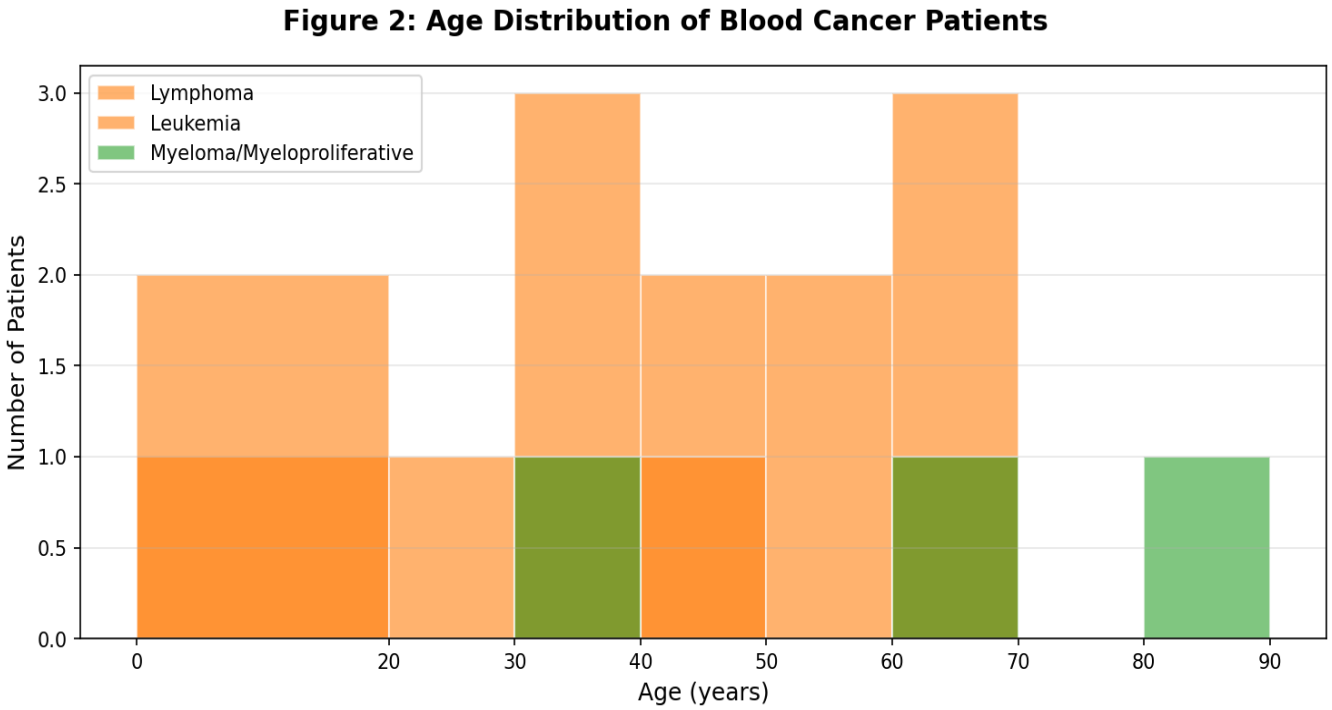

Figure 2: Age distribution of blood cancer patients stratified by cancer category (bin width = 10 years).

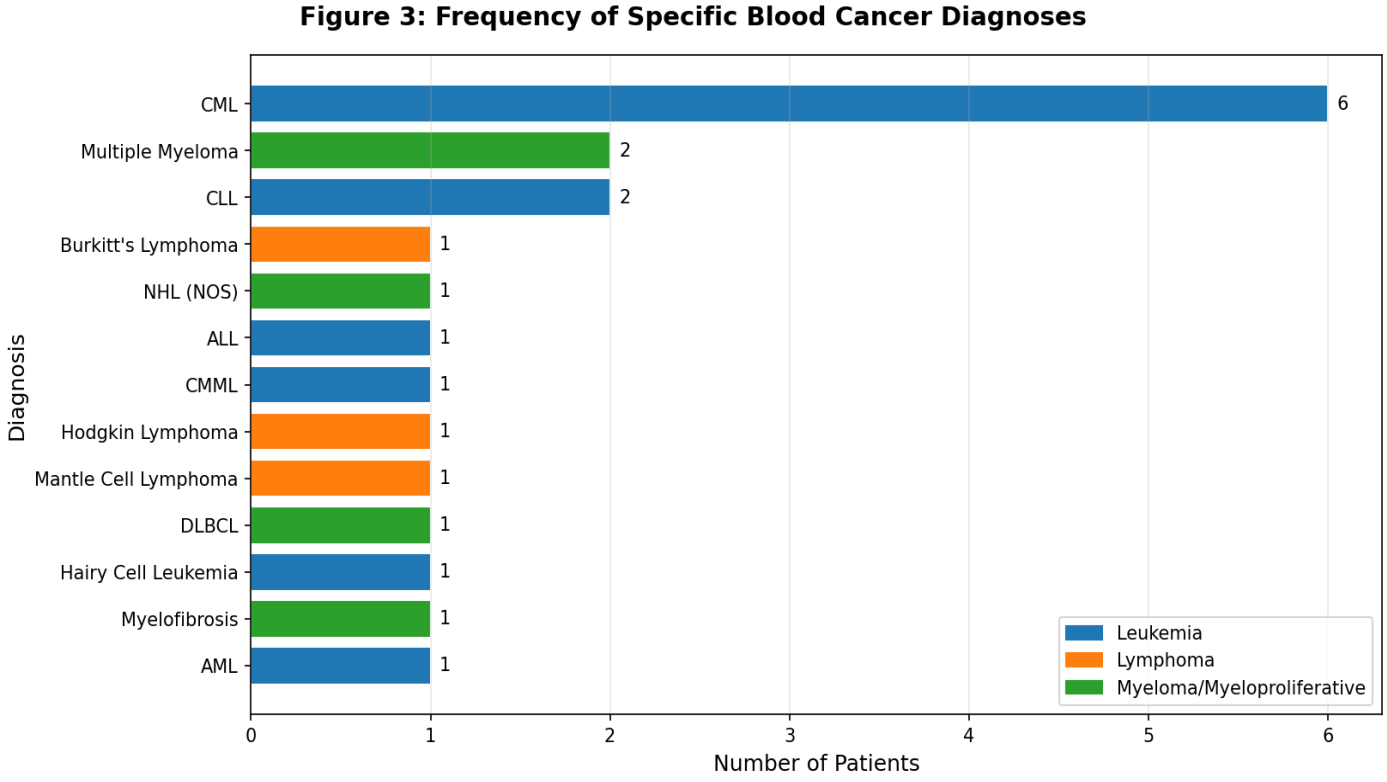

Figure 3: Horizontal bar chart depicting frequency of each specific blood cancer diagnosis. Blue = Leukemia; Orange = Lymphoma; Green = Myeloma/MPD.

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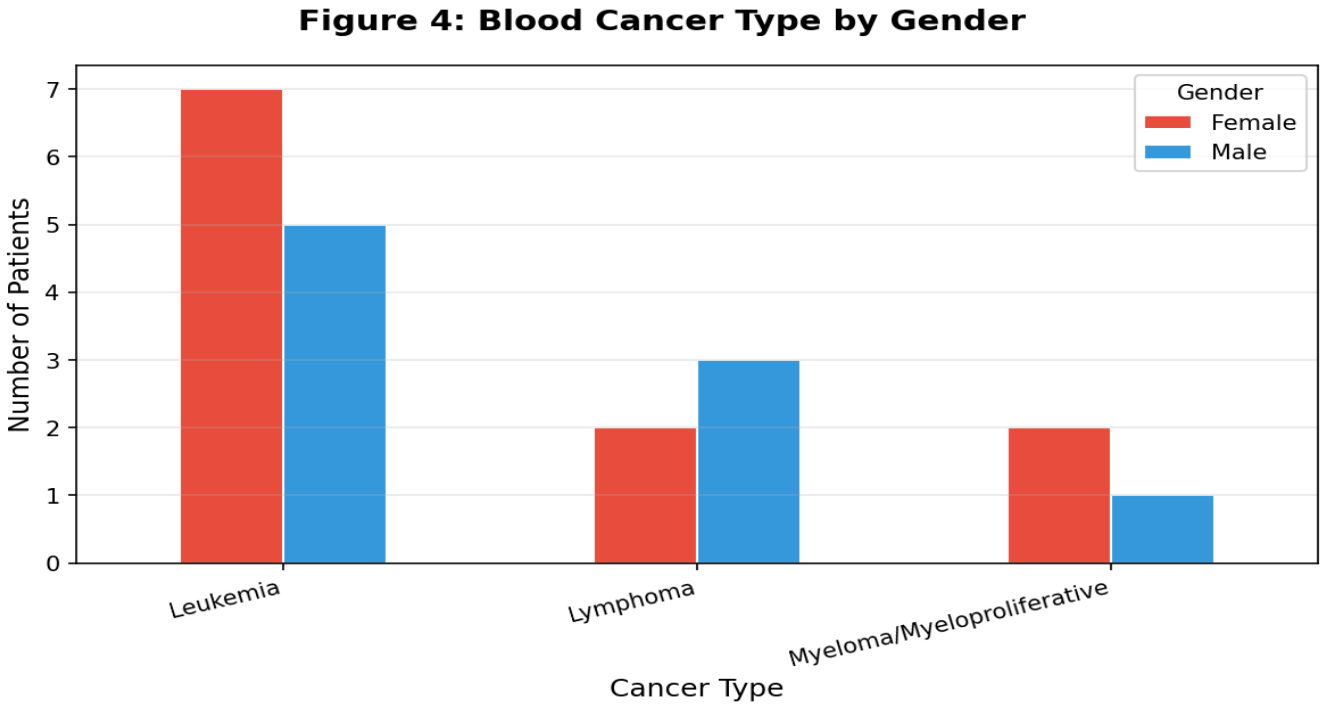

Figure 4: Grouped bar chart showing gender distribution across the three major blood cancer categories.

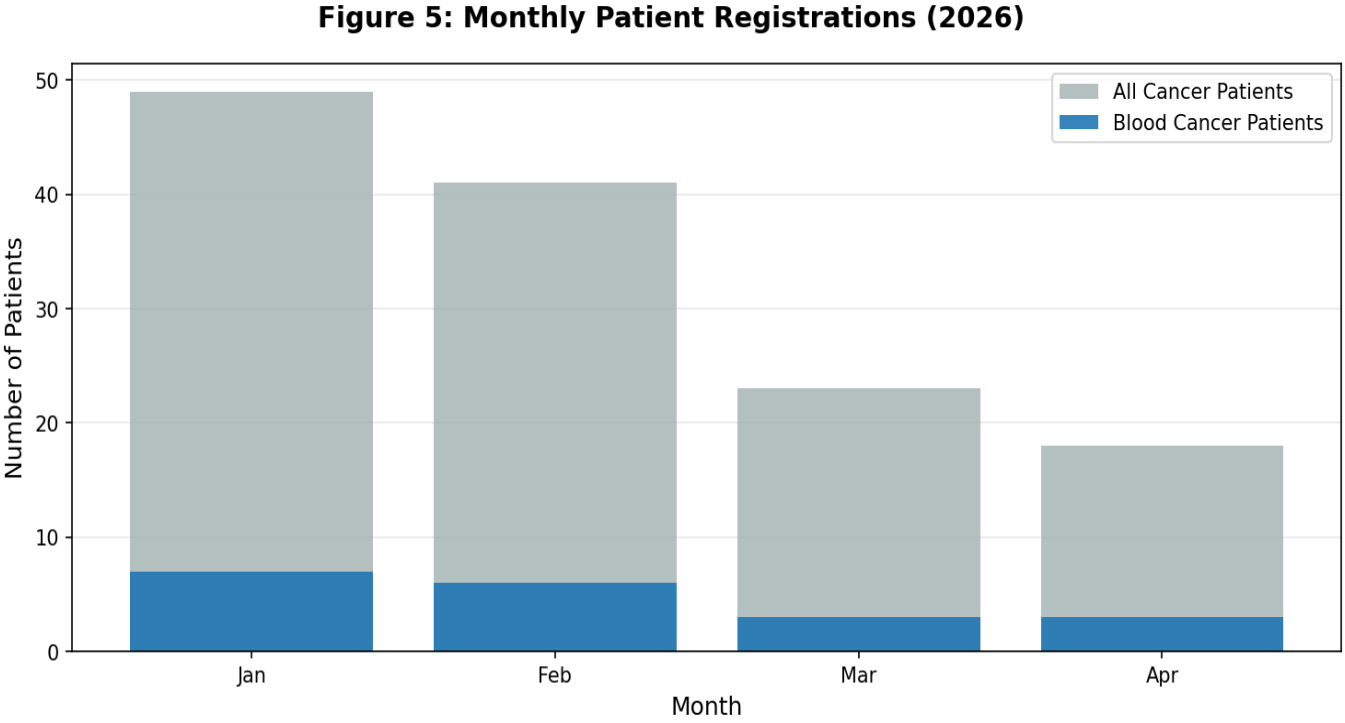

Figure 5: Monthly patient registrations from January to April 2026. Grey bars = all cancer patients; Blue bars = blood cancer patients.

3.6 Referral Patterns

Among blood cancer patients with documented referral information, self-referral was the most common source (n=5, 25.0%), followed by various medical outpatient and surgery departments. Several patients were referred from peripheral district hospitals including THQ Taxila, DHQ Jhelum, and Talagang, reflecting the wide geographic catchment area of the UOC. Internal medicine wards (Medicine OPD) accounted for 2 referrals, while 1 patient was from the dedicated CML clinic within the same institution.

3.7 Clinical Outcomes

Formal outcome data were available for a subset of patients, as many were still under active follow-up or awaiting workup results at the time of data extraction. Among documented outcomes, 1 patient (5.0%) was recorded as deceased (expired), 1 was referred to Shaukat Khanum Memorial Cancer Hospital for specialised treatment, and 1 was enrolled in the institutional CML clinic for chronic disease management. Several patients were referred to NORI (Nuclear Medicine, Oncology and Radiotherapy Institute, Islamabad) or tertiary academic centres for definitive chemotherapy, radiation, or bone marrow evaluation. The limited outcome documentation reflects the short follow-up window of this study period.

4. Discussion

This retrospective analysis of UOC registration data from January to April 2026 reveals that haematological malignancies constitute a clinically significant component of the oncology workload at Holy Family Hospital, Rawalpindi—accounting for 15.0% of all new registrations. This is broadly consistent with international estimates suggesting that blood cancers represent 6–10% of new cancer diagnoses, though single-centre tertiary referral data often yield higher proportions due to the selective nature of referrals to specialised units [2].

The dominance of CML (30.0% of all blood cancers) is a striking finding that echoes patterns described in earlier studies from Pakistan and South Asia. A national-level analysis from the Shaukat Khanum Memorial Cancer Hospital registry identified CML as the most common haematological malignancy in Pakistan, a pattern attributed to the young demographic structure of the population, relatively long survival with BCR-ABL inhibitors (enabling prevalent cases to accumulate in clinical registers), and, potentially, undiagnosed/environmentally influenced disease [6]. Importantly, 6 of 20 blood cancer patients in our dataset carried a CML diagnosis, with a wide age range (17–62 years), including a 17-year-old male. This underscores the importance of maintaining CML surveillance clinics and ensuring uninterrupted access to tyrosine kinase inhibitors (TKIs) such as imatinib and nilotinib for patients across income strata.

The epidemiology of lymphomas in this cohort is particularly noteworthy. Burkitt's Lymphoma, a highly aggressive B-cell NHL typically requiring prompt initiation of intensive chemotherapy, was identified in a 39-year-old male. In Pakistan, Burkitt's Lymphoma predominantly presents in sporadic (non-endemic) form and is associated with a significant diagnostic and management challenge in resource-limited settings given its rapid doubling time and need for CNS prophylaxis [7]. Similarly, Diffuse Large B-Cell Lymphoma (DLBCL) and Mantle Cell Lymphoma—both aggressive NHL subtypes with distinct immunophenotypic and molecular profiles—were represented in the cohort, reflecting the diagnostic complexity of haematological oncology in this setting.

The identification of a Hodgkin Lymphoma case in a 19-year-old female is consistent with the well-described bimodal age distribution of this disease, with a characteristic peak in young adults. Hodgkin Lymphoma is notable for its high curability (>80% long-term survival in early-stage disease with appropriate chemoradiotherapy), making accurate diagnosis and timely referral critically important [8].

Among the myeloma/myeloproliferative group, the presence of Multiple Myeloma in an 82-year-old female and Myelofibrosis in a 66-year-old male is consistent with the well-established late-onset epidemiology of these conditions. Multiple Myeloma is characterised by clonal proliferation of plasma cells in the bone marrow and is predominantly a disease of older adults (median age at diagnosis ~65 years globally) [9]. The challenge of providing novel therapeutic agents—including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies—in the Pakistani healthcare context, where out-of-pocket expenditure dominates, is a critical area for policy attention.

Gender analysis showed a female predominance (55.0%) across the blood cancer cohort, which differs from most global datasets where slight male predominance is reported for leukemia and myeloma [10]. This finding may reflect differences in healthcare-seeking behaviour, referral biases, or genuine regional epidemiological variation, and warrants further investigation with larger cohorts.

The age distribution data (Figure 2) reveal a bimodal pattern: a younger peak predominantly comprising leukemia cases (CML, ALL) in the 17–45-year age bracket, and an older peak of myeloma/MPD cases in the 60+ age bracket. This pattern has direct implications for workforce productivity loss associated with blood cancers, as the younger age group represents individuals of peak earning capacity.

Limitations of this study include its retrospective single-centre design, short study window (4 months), small sample size for subgroup analyses, and incomplete outcome data due to ongoing follow-up. Additionally, some diagnoses were recorded as presumptive or differential rather than confirmed via biopsy and immunophenotyping, which may have affected classification accuracy. Future research should aim to establish a prospective, multi-centre haematological malignancy registry for northern Pakistan.

5. Conclusions

Blood cancers account for a substantial 15.0% of oncology registrations at the UOC, Holy Family Hospital, Rawalpindi, with leukemia—particularly CML—being the predominant category. The demographic profile reveals a wide age range (15–82 years), female predominance, and a geographically diverse catchment area spanning multiple districts of northern Punjab. These findings highlight the need for dedicated haematology clinics, point-of-care diagnostic capacity (including BCR-ABL PCR, bone marrow biopsy services, and flow cytometry), and sustainable access to targeted therapies including tyrosine kinase inhibitors.

Establishing a prospective, population-based haematological malignancy registry for Pakistan remains an urgent public health priority. Such a registry would enable accurate burden estimation, facilitate clinical research, and support evidence-based policy development to reduce morbidity and mortality associated with blood cancers in this resource-constrained setting.

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Original Article

Tumor Biology and Molecular Pathology of Hepatic Malignancies in Northern Pakistan: Cirrhosis-Driven Hepatocarcinogenesis, Portal Vein Invasion, Multifocal Disease, Neuroendocrine Differentiation, and Biliary Subtypes — A Real-World Cohort Study from the RMU Disease Data Centre, 2026

Abstract

Background: Hepatocellular carcinoma (HCC) in Pakistan arises predominantly on the substrate of hepatitis C virus (HCV)-related cirrhosis, but its molecular and pathological heterogeneity — encompassing cirrhosis-driven hepatocarcinogenesis, portal vein tumor thrombus (PVTT), multifocal disease, and rare histological variants such as neuroendocrine carcinoma (NEC) and hilar cholangiocarcinoma — remains poorly characterized in real-world Pakistani patient cohorts. Molecular insights derived from registry-level clinical and radiological data can complement formal molecular profiling to guide treatment stratification.

Objectives: To characterize the tumor biology and molecular-pathological landscape of liver malignancies at the RMU Oncology Clinic, with specific focus on: (i) the role of cirrhosis and its aetiology in HCC development; (ii) tumor morphology including multifocal and infiltrative patterns; (iii) portal vein tumor thrombus as a molecular and vascular event; (iv) neuroendocrine differentiation in hepatobiliary tumors; and (v) biliary tract subtype characterization.

Methods: Retrospective molecular-pathological analysis of 16 liver malignancy cases from the RMU Disease Data Centre (DDC) registry, January–April 2026. Clinical, radiological, biochemical, and histopathological data were extracted and classified by tumor biology subgroup. BCLC staging was applied where data permitted. Child-Pugh scoring, tumor markers (AFP, PIVKA-II, CA 19-9), CT morphology, IHC findings (where available), and clinical trajectory were synthesized to construct tumor biology profiles.

Results: Of 12 HCC patients, 75% presented at BCLC stage C or D (advanced/end-stage), with multifocal disease in 4 (33.3%) and PVTT in 1 (8.3%). Cirrhosis was the underlying substrate in 10/12 HCC cases (83.3%): HCV in 5, HBV in 1, and cryptogenic/unknown in 4. Notably, 3 patients developed HCC after documented HCV eradication with direct-acting antivirals (DAA), confirming persistent hepatocarcinogenic risk post-SVR. Liver function was severely compromised: Child-Pugh C or decompensated disease was present in 4 formally assessed patients. AFP exceeded 80,000 IU/mL in one patient (UOC-973). Among non-HCC malignancies, one case of hilar cholangiocarcinoma (CCA) with porta hepatis mass encasing the hepatic artery was confirmed on CT, and one case of hepatobiliary neuroendocrine carcinoma (NEC) was confirmed on immunohistochemistry (synaptophysin/chromogranin-A positive, CA 19-9 8,020 U/mL). Gallbladder carcinoma with liver infiltration was present in 2 additional patients.

Conclusions: The molecular-pathological landscape of liver malignancies in this northern Pakistani cohort is dominated by HCV-driven cirrhosis-to-HCC progression, with an alarming proportion of post-SVR HCC cases indicating ongoing hepatocarcinogenesis despite viral clearance. Advanced-stage multifocal disease and compromised hepatic reserve are characteristic of this population. Rare entities — NEC and hilar CCA — require mandatory IHC and structured biliary imaging protocols. These findings underscore the urgent need for post-SVR HCC surveillance, standardized molecular staging, and a multidisciplinary liver tumor board at RMU/HFH.

Keywords: *Hepatocellular carcinoma; tumor biology; cirrhosis; HCV; portal vein thrombus; multifocal HCC; BCLC staging; neuroendocrine carcinoma; cholangiocarcinoma; molecular pathology; Pakistan; RMU Disease Data Centre*

1. Introduction

Liver cancer is the sixth most incident and third most lethal cancer worldwide, with hepatocellular carcinoma (HCC) accounting for 75–85% of primary liver malignancies [1]. The molecular biology of HCC is characterized by extraordinary heterogeneity: while cirrhosis is the shared final pathway for the vast majority of HCC cases regardless of aetiology, the molecular landscape of HBV-driven HCC differs significantly from HCV-related, alcohol-related, or metabolic-associated (MASH/NASH-related) carcinogenesis [2]. Understanding Tumor biology — growth pattern, vascular invasion, genomic instability, and histological subtype — is increasingly central to treatment selection in the era of targeted therapy and immune checkpoint inhibition [3].

Pakistan faces a unique hepatocarcinogenic environment. With an HCV prevalence of 4.7–6.7% nationally (estimated 10–12 million infected individuals) [4] and a rising burden of type 2 diabetes and metabolic syndrome, the country is positioned at the intersection of the two most rapidly growing global drivers of HCC. Unlike high-income settings where early-stage HCC is increasingly identified through surveillance programs, the vast majority of Pakistani patients present with advanced disease [5], implying that hepatocarcinogenesis has proceeded through multiple molecular stages before clinical detection.

Beyond classical HCC, the liver is a common site of involvement for biliary tract malignancies, including hilar cholangiocarcinoma (Klatskin tumor), gallbladder carcinoma with hepatic infiltration, and the rare but increasingly recognized hepatobiliary neuroendocrine carcinoma (NEC). Each carries a distinct molecular biology, diagnostic paradigm, and therapeutic implication [6,7].

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

Original Article

The RMU Disease Data Centre, established at Holy Family Hospital (HFH), provides a prospectively maintained oncology registry from one of Pakistan's highest-volume public-sector tertiary care centers. This paper analyses the tumor biology and molecular-pathological features of all liver malignancy cases registered during January–April 2026, focusing specifically on cirrhosis substrate, tumor morphology, vascular invasion, histological variants, and the molecular implications of post-SVR HCC.

2. Background: molecular pathways to hepatic malignancy

2.1 The Cirrhosis–HCC Axis

Cirrhosis represents the critical microenvironmental substrate for the majority of HCC cases globally. The sequence from chronic hepatocellular injury → inflammation → fibrosis → cirrhosis → dysplastic nodule → early HCC → overt HCC is well characterized at the molecular level [2]. Key oncogenic events during this progression include: telomere shortening and chromosomal instability, activation of the Wnt/β-catenin pathway (mutations in CTNNB1, ~25–30% of HCC), TP53 inactivation (particularly in aflatoxin B1-exposed and HBV-related HCC), and activation of the Ras/MAPK and PI3K/AKT/mTOR axes [2,8]. HCV-related hepatocarcinogenesis is additionally driven by the direct oncogenic properties of the HCV non-structural protein NS5A, which disrupts apoptosis, promotes cell proliferation, and induces oxidative stress independently of cirrhosis [9].

In patients who achieve sustained virological response (SVR) with DAA therapy, HCV replication ceases but the epigenetic and genomic alterations accumulated during decades of chronic infection — including aberrant DNA methylation patterns, telomere attrition, and clonal hepatocyte expansion — persist in the cirrhotic microenvironment [10]. This molecular 'memory' of HCV infection explains why HCC risk, while reduced by 71–75% following SVR, is not eliminated in patients with established cirrhosis [11]. Three patients in this cohort developed HCC despite documented HCV eradication, providing direct clinical evidence of this molecular phenomenon.

2.2 Portal Vein Tumor Thrombus: A Molecular Vascular Event

Portal vein tumor thrombus (PVTT) in HCC represents active vascular invasion by tumor cells and is a defining feature of BCLC stage C disease [5]. At the molecular level, PVTT is associated with upregulation of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-9, and epithelial-mesenchymal transition (EMT) markers — the same molecular pathways targeted by lenvatinib and sorafenib [3,12]. PVTT is present in 10–40% of HCC at diagnosis and is associated with a median overall survival of 2–5 months in untreated patients [13]. The single PVTT case in this cohort (UOC-1029) presented with multifocal disease, large portal thrombus (7.2×7.0 cm largest lesion), ascites, and prior HCV infection, representing the most molecularly advanced case in the series.

2.3 Neuroendocrine Carcinoma of the Hepatobiliary System

Primary hepatobiliary NEC is a rare entity, comprising <1% of primary liver malignancies [7]. Poorly differentiated NEC (WHO Grade 3, Ki-67 >20%) of the hepatobiliary system is biologically aggressive, with a molecular profile characterised by ASCL1/NEUROD1 expression, RB1 loss, TP53 mutations, and MYCL amplification — similar to small-cell lung cancer [7,14]. CA 19-9 can be markedly elevated in NEC, particularly large-cell type, creating potential diagnostic confusion with biliary malignancy before IHC confirmation. The NEC case in this series (UOC-1004) had CA 19-9 of 8,020 U/mL, a prior history of cholecystectomy 25 years earlier, and CT showing a gallbladder fossa mass infiltrating the liver — ultimately confirmed as NEC by synaptophysin and chromogranin A positivity on IHC.

2.4 Hilar Cholangiocarcinoma: Biliary Epithelial Malignancy

Hilar cholangiocarcinoma (Klatskin tumor) arises at the confluence of the right and left hepatic ducts, with a molecular landscape characterized by KRAS, IDH1/2, FGFR2, and SMAD4 alterations [6]. The porta hepatis location of the mass in UOC-1002 (3.1×3.7×3.8 cm mass causing abrupt hepatic duct cutoff, encasing the common hepatic artery >180°) on CT is pathognomonic for Bismuth-Corlette type IIIA or IV hilar CCA. IDH1 mutation — present in ~15–20% of CCA — confers sensitivity to ivosidenib, now approved for IDH1-mutant CCA [6].

3. Materials and methods

3.1 Study Design and Data Source

Retrospective molecular-pathological cohort analysis of 16 liver malignancy cases registered in the RMU DDC Oncology Clinic registry, HFH, Rawalpindi, during January 1 – April 14, 2026. The RMU DDC is a prospectively maintained registry capturing demographic, clinical, radiological, biochemical, and treatment data at each patient encounter.

3.2 Data Extraction and Molecular Subgroup Classification

Tumor biology variables extracted: (i) underlying hepatic substrate (HCV cirrhosis, HBV cirrhosis, cryptogenic cirrhosis, non-cirrhotic); (ii) HCC morphological pattern (solitary nodular <5 cm, solitary nodular ≥5 cm, multifocal, infiltrative with PVTT); (iii) Child-Pugh score (A/B/C); (iv) BCLC stage (A/B/C/D); (v) AFP, PIVKA-II, CA 19-9 values; (vi) CT imaging features (LI-RADS major features, PVTT, ascites, splenomegaly, lymphadenopathy); (vii) IHC results where available. For cases with insufficient histopathological data, molecular characterization was inferred from CT morphology, biomarker profile, clinical context, and comparison with published molecular correlates.

3.3 BCLC Staging

Barcelona Clinic Liver Cancer (BCLC) staging [5] was applied to all 12 HCC cases using: tumor number and size (CT-derived), PVTT status, AFP, Child-Pugh class, ECOG performance status (clinician-assessed), and extrahepatic spread. Where complete staging data were unavailable, conservative (higher-stage) classification was applied, consistent with EASL 2018 guidance [5].

3.4 Statistical Analysis

Descriptive statistics with frequency counts and proportions. Continuous data reported as median with range. No inferential statistics applied given the small cohort size and descriptive purpose. All patient data were fully anonymized.

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4. Results

4.1 Histological Subtype Distribution

Of the 16 liver malignancy patients, 12 (75.0%) had confirmed or strongly suspected HCC, 1 (6.3%) hilar cholangiocarcinoma, 1 (6.3%) hepatobiliary NEC (IHC-confirmed), 2 (12.5%) gallbladder carcinoma with liver infiltration, and 2 (12.5%) hepatic metastases from a GI primary. Three patients had an 'atypical HCC' designation indicating diagnostic uncertainty (CT features not classic, biopsy pending or refused). Figure 6 and Table 1 summarize the full histological distribution.

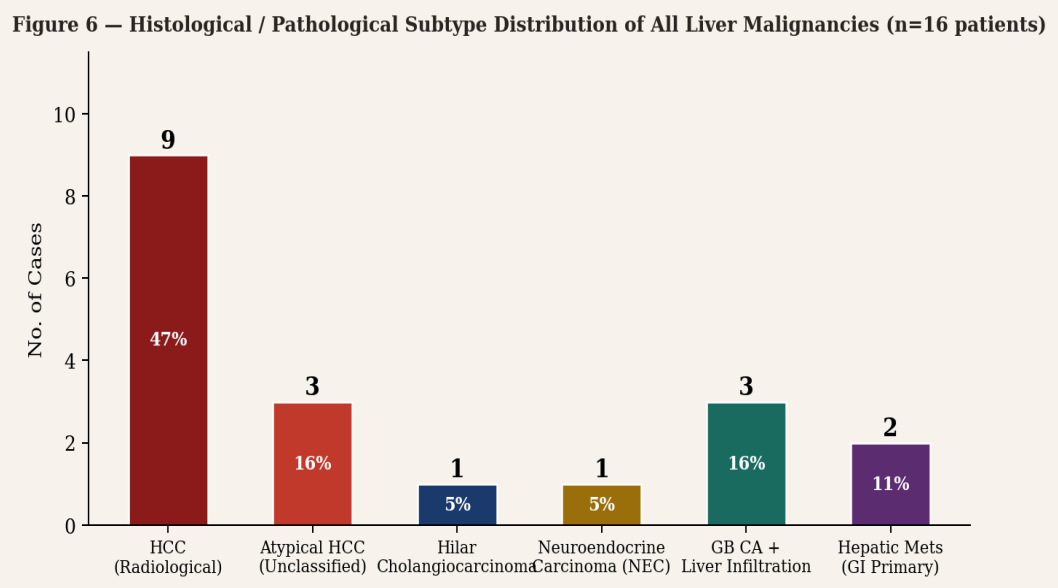

Figure 6 — Histological and Pathological Subtype Distribution of All Liver Malignancies (n=16 patients, 19 Tumor diagnoses including composite subtypes)

Table 1 — Tumor Biology Subgroup Classification of All Liver Malignancy Cases (RMU DDC, Jan–Apr 2026)

Reg No.	Diagnosis	BCLC Stage	Child-Pugh	Cirrhosis Substrate	Molecular / Pathological Feature
UOC-915	CCA vs Atypical HCC	C (provisional)	NF	Unknown	Biopsy referred CMH; diagnostic uncertainty CCA vs. HCC
UOC-916	Atypical HCC	C (disease progression)	NF	Unknown	Prior NORI treatment; disease progression on therapy
UOC-918	HCC (confirmed)	B/C	NF	Unknown	Lenvatinib initiated; baseline CT data incomplete
UOC-931	HCC (confirmed)	C	NF	Unknown	Lenvatinib 8→12 mg/day; PBM; blood transfusion needed
UOC-940	HCC	D	NF	Unknown	BSC only; HCC clinic follow-up; no oncological treatment
UOC-945	HCC / Hepatoma	C/D	NF (referred gastro)	Unknown	BSC; Child-Pugh calculation deferred to gastroenterology
UOC-969	HCC	B (provisional)	NF	Unknown	Workup in progress; 50F; early age of onset
UOC-973	HCC (confirmed)	C	A (score 5)	Unknown	AFP 80,000; lenvatinib; ALP 159.6 — Child-Pugh A (best documented)
UOC-975	HCC	D	NF	Unknown	BSC; financial support PKR 12,000; 77y male
UOC-997	HCC (confirmed)	B/C	NF	Unknown	Lenvatinib 8mg OD via BTM after 47-day delay; PIVKA-II ordered
UOC-1001	HCC on DCLD	C	C (DCLD)	HCV (SVR-5yrs)	Post-DAA HCC on established cirrhosis; referred for TACE

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Reg No.	Diagnosis	BCLC Stage	Child-Pugh	Cirrhosis Substrate	Molecular / Pathological Feature
UOC-1005	HCC (confirmed)	C	C (DCLD)	HCV (recent DAA)	Arterialized CT lesions + washout; DCLD; BSC only
UOC-1007	HCC (confirmed)	C	NF	HCV (SVR-2024)	12.1 cm mass Segs V&VI; post-SVR HCC; 75F; hookah smoker
UOC-1019	HCC (suspected)	Unknown	NF	Unknown	Lost to follow-up; 56y male; AFP and CT pending
UOC-1023	HCC (suspected, HBV+)	B/C	NF (albumin 2.5)	HBV	AFP 558; HBV+; raised creatinine delaying CT
UOC-1029	HCC multifocal + PVTT	C	NF	HCV (SVR-7yrs)	7.2×7.0 cm largest; portal vein thrombus; ascites; DM; naswar
UOC-1002	Hilar CCA	C	NF	None	Porta hepatis 3.8 cm; >180° hepatic artery encasement; ERCP+stenting
UOC-1004	Hepatobiliary NEC	C	NF	None	CA 19-9 8,020; IHC: NEC confirmed; lung nodules; PIMS surgery
UOC-1039	GB CA + hepatic mets	D	NF	HCV (treated)	AFP 1,000; ALP 569; advanced hepatic involvement; BSC
UOC-1043	GB CA + liver infiltration	C/D	NF	None	Jaundice, fever, SOB; Gastro ward admission

NF=Not formally scored. BSC=best supportive care. DCLD=decompensated chronic liver disease. SVR=sustained virological response. PVTT=portal vein Tumor thrombus. BTM=Bait ul Mal. CCA=cholangiocarcinoma. NEC=neuroendocrine carcinoma. ERCP=endoscopic retrograde cholangiopancreatography. GB=gallbladder. ALP in IU/L. AFP in IU/mL. CA 19-9 in U/mL.

4.2 BCLC Staging Distribution

BCLC staging was formally applied to 12 HCC cases (Figure 1). The distribution was markedly skewed toward advanced disease: BCLC C (advanced) was the most common stage (n=6, 50%), followed by BCLC D (end-stage, n=3, 25%), BCLC B (intermediate, n=2, 16.7%), and BCLC A (early, n=1, 8.3%). The predominance of BCLC C–D disease (75% of cases) reflects the combination of late clinical presentation and the underlying severity of decompensated cirrhosis in this cohort, consistent with global LMIC data showing 70–80% of HCC presenting at BCLC C/D in settings without active surveillance programs [5].

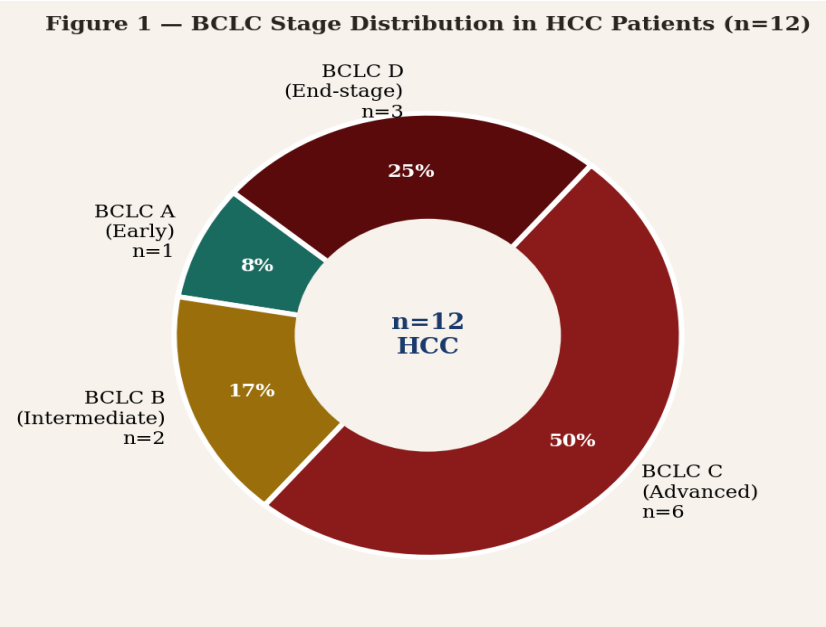

Figure 1 — BCLC Stage Distribution in HCC Patients (n=12), RMU Disease Data Centre, Jan–Apr 2026

4.3 Molecular Subgroup Classification

Figure 2 presents the molecular/pathological subgroup classification of liver malignancies. HCC on HCV-related cirrhosis was the largest subgroup (n=5, 41.7% of HCC), followed by HCC on cryptogenic/unknown-aetiology cirrhosis (n=4, 33.3%), HCC on HBV cirrhosis (n=1, 8.3%), and non-cirrhotic HCC (n=2, 16.7%). Multifocal HCC (two or more lesions) was documented in 4 patients (33.3%). GB carcinoma with liver infiltration accounted for 2 cases; NEC and hilar CCA accounted for one each.

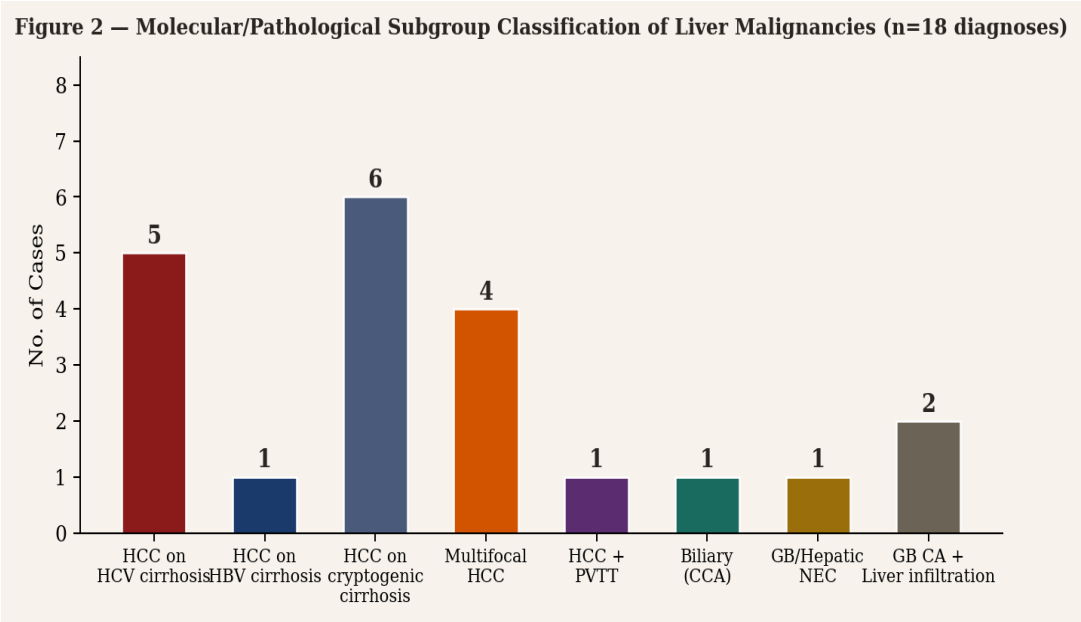

Figure 2 — Molecular/Pathological Subgroup Classification of Liver Malignancies (n=18 Tumor diagnoses)

4.4 Cirrhosis Substrate and Child-Pugh Liver Function

Cirrhosis was the underlying hepatic substrate in 10 of 12 HCC patients (83.3%) (Figure 3). HCV was the most common aetiological driver (5 patients, 41.7%), with HBV in 1 (8.3%) and cryptogenic/unknown cirrhosis in 4 (33.3%). Notably, three of the HCV-positive patients (UOC-1001, UOC-1007, UOC-1029) had documented prior DAA therapy with PCR-negative (SVR) status, developing HCC a median of 5–7 years after viral clearance. This subgroup — post-SVR HCC on established cirrhosis — represents the most clinically alarming molecular subgroup in this cohort.

Child-Pugh scoring was formally documented in 4/12 HCC patients (33.3%). UOC-973 was Child-Pugh A (score 5) — the only patient with complete and explicitly documented LFT-based scoring, enabling lenvatinib initiation per REFLECT trial criteria [15]. Patients UOC-940, UOC-945, UOC-975, and UOC-1005 demonstrated clinical features of Child-Pugh C (decompensated) disease (ascites, jaundice, or encephalopathy implied), which precluded systemic oncological therapy. The Child-Pugh distribution highlights that hepatic decompensation, rather than Tumor burden alone, was the primary determinant of treatment ineligibility in this cohort.

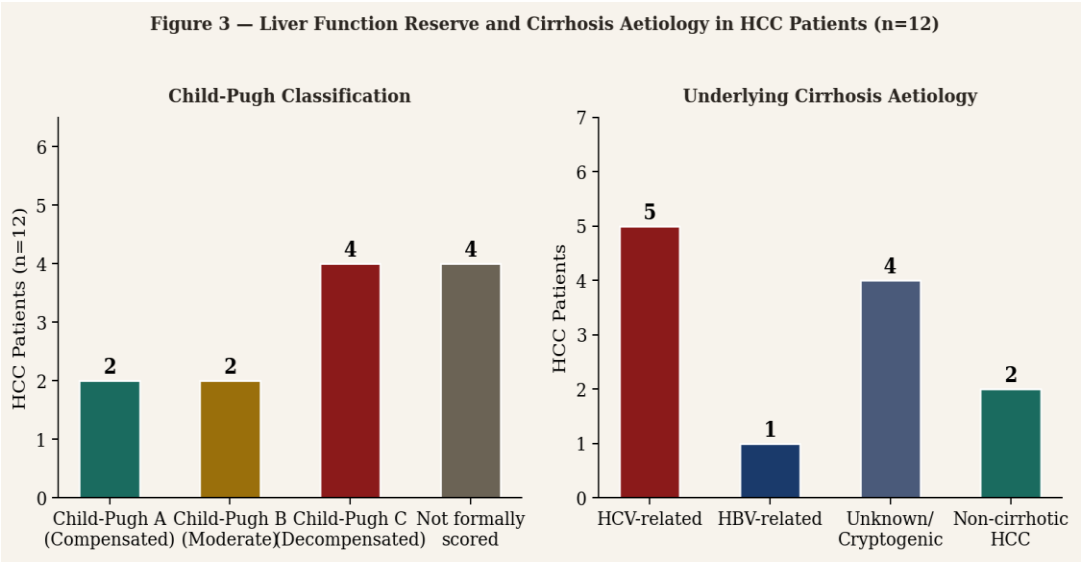

Figure 3 — Child-Pugh Classification (left) and Underlying Cirrhosis Aetiology (right) in HCC Patients (n=12)

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4.5 Tumor Morphology and Growth Pattern

CT-derived Tumor morphology was classified into five categories (Figure 4). Multifocal disease (two or more distinct hepatic lesions) was present in 4 patients (33.3%) and represents the most common advanced morphological pattern, consistent with the known proclivity of HCC for intrahepatic dissemination via portal venous branches [2]. Solitary large Tumors (≥5 cm) were present in 3 patients (25.0%), including UOC-1007 with a 12.1×12.1 cm mass occupying segments V and VI — one of the largest Tumors in this series. Infiltrative HCC with PVTT (UOC-1029) represented the most aggressive morphological subtype: CT showed "multiple well-defined arterialized infiltrative lesions... with washout on portovenous and delayed phase... large Tumor thrombus in the portal vein," the largest lesion measuring 7.2×7.0 cm.

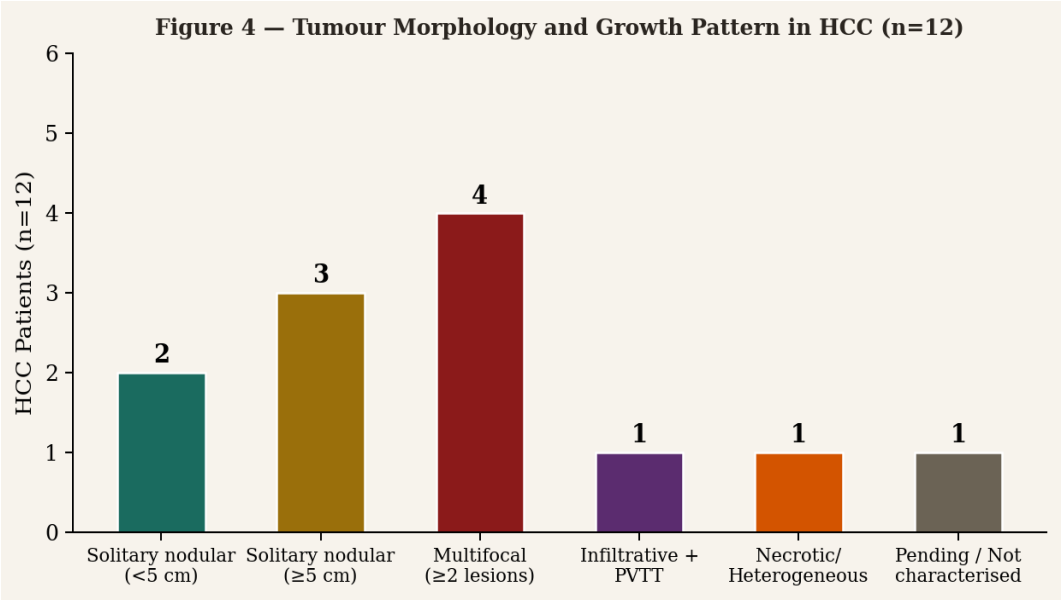

Figure 4 — Tumor Morphology and Growth Pattern on CT Imaging in HCC Patients (n=12)

Table 2 — CT Tumor Morphology and Radiological Molecular Correlates in HCC Patients

Reg No.	Tumor Pattern	Largest Lesion (cm)	Segments Affected	PVTT / Vascular Inv.	Molecular Correlate / Comments
UOC-973	Solitary (presumed)	NR	Not specified	No	AFP 80,000 IU/mL; Child-Pugh A; lenvatinib responsive
UOC-1005	Multifocal necrotic	NR	Right lobe	No	DCLD background; necrotic core; arterialized enhancement with washout
UOC-1007	Solitary large	12.1	V & VI	No	12.1 cm; classic APHE + washout; post-SVR HCC; 75F; hookah
UOC-1029	Infiltrative multifocal	7.2×7.0	Both lobes	Yes (PVTT)	PVTT; DM+Naswar; ascites; BCLC C; worst vascular profile
UOC-1001	Unknown (DCLD)	NR	NR	No	HCC on established DCLD; post-DAA SVR 5 yrs; TACE referred
UOC-931	Not documented	NR	NR	No	Lenvatinib started; PBM; blood transfusion required later
UOC-918	Not documented	NR	NR	No	Lenvatinib 12 mg initiated; baseline CT not reported in notes
UOC-940	Not documented	NR	NR	No	BSC; HCC clinic; no systemic treatment; likely BCLC D
UOC-945	Not documented	NR	NR	No	BSC; Child-Pugh deferred; hepatoma clinical diagnosis
UOC-975	Not documented	NR	NR	No	77y M; BSC; financial support; BCLC D (clinical)

Reg No.	Tumor Pattern	Largest Lesion (cm)	Segments Affected	PVTT / Vascular Inv.	Molecular Correlate / Comments
UOC-997	Not documented	NR	NR	No	CT pending 47 days post-registration; lenvatinib BTM initiated
UOC-1023	Not documented	NR	NR	No	HBV+; AFP 558; raised creatinine delaying CT triphasic

NR=Not reported. PVTT=portal vein Tumor thrombus. APHE=arterial phase hyperenhancement. DCLD=decompensated chronic liver disease. AFP in IU/mL. BSC=best supportive care. BTM=Bait ul Mal.

4.6 Portal Vein Tumor Thrombus: Case Analysis

PVTT was confirmed on CT in one patient (UOC-1029, 65y male). The CT report explicitly stated: "Large tumor thrombus in the portal vein" alongside "multiple well-defined arterialized infiltrative lesions in both right and left lobe of the liver showing washout on portovenous and delayed phase." This constellation — bilobar multifocal HCC with main portal vein thrombus — is classified as BCLC C advanced disease and confers a median untreated survival of 2–4 months [13].

Molecularly, PVTT in HCC is driven by upregulation of VEGF-A, angiopoietin-2, and MMP-9, facilitating Tumor invasion through the sinusoidal endothelium into the portal venous system [12]. The co-existing metabolic risk factors in UOC-1029 (diabetes mellitus for 6 years, naswar addiction, post-HCV cirrhosis) create a profoundly pro-oncogenic hepatic microenvironment through hyperinsulinaemia-driven IGF-1 signalling, oxidative tobacco carcinogens, and residual epigenetic HCV imprinting. Lenvatinib and sorafenib both demonstrate efficacy in BCLC C HCC with PVTT, with lenvatinib showing superior response rate (24.1% vs 9.2%) in the REFLECT trial [15], but this patient had not yet initiated systemic therapy at the time of data closure.

KEY MOLECULAR FINDING — POST-SVR HCC

Three of 12 HCC patients (25%) in this cohort developed HCC despite documented HCV eradication with DAA therapy (SVR confirmed by PCR negativity, 5–7 years prior). None were enrolled in any post-SVR surveillance program. This represents direct clinical evidence of persistent hepatocarcinogenesis after viral clearance, driven by the molecular 'memory' of HCV in the cirrhotic epigenome. Lifelong 6-monthly surveillance is mandatory in all post-SVR cirrhosis patients.

4.7 The Child-Pugh A Exception: UOC-973 — A Detailed Molecular Profile

UOC-973 (70y male) represents the most molecularly well-characterised patient in this cohort and serves as the internal benchmark for treatment-eligible HCC in this series. AFP of 80,000 IU/mL — the highest in the cohort — is consistent with the molecular signature of AFP-high HCC, which is associated with enrichment of foetal hepatocyte gene expression, lower Wnt/β-catenin pathway activity, and higher vascular invasiveness [2]. However, the preserved hepatic function (Child-Pugh A, score 5; bilirubin 0.8, albumin 4.1, PT/INR 1.0) placed this patient in the optimal therapeutic window for first-line lenvatinib.

The complete biochemical profile of UOC-973 (Figure 5) demonstrates: normal bilirubin (0.8 mg/dL), near-normal ALT (19.9 IU/L; below upper limit), mildly elevated ALP (159.6 IU/L; just above ULN of 147), normal albumin (4.1 g/dL), normal platelet count (315×10³/µL), and normal PT/INR (13/1.0). This profile, despite an AFP of 80,000 IU/mL, illustrates that very high AFP can coexist with preserved synthetic function, particularly in patients whose HCC has developed on compensated cirrhosis rather than florid hepatic decompensation. The paradox of high Tumor burden with preserved hepatic function reflects the focal rather than diffuse nature of early HCC relative to the cirrhotic background parenchyma.

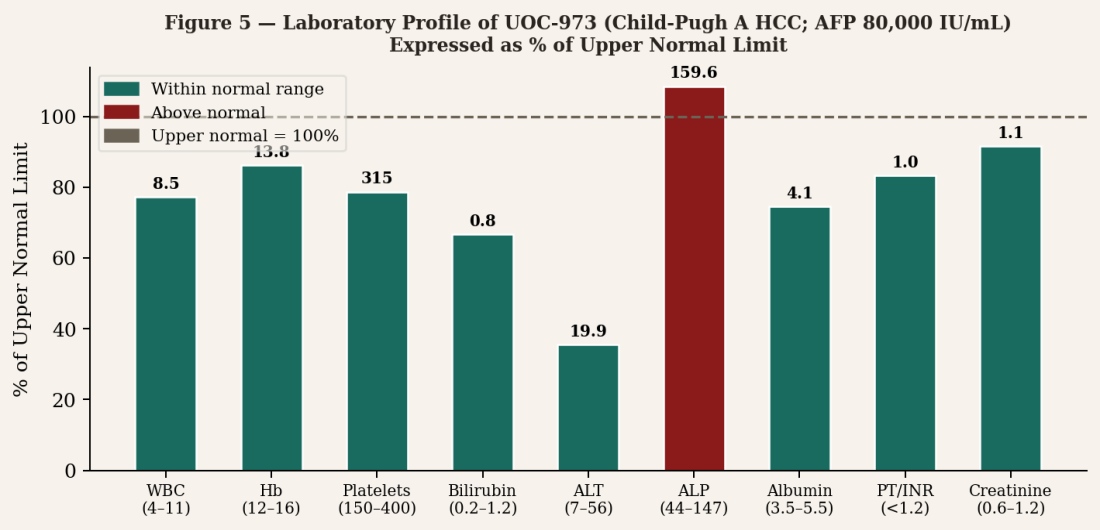

Figure 5 — Laboratory Profile of UOC-973 (Child-Pugh A HCC; AFP 80,000 IU/mL) Expressed as % of Upper Normal Limit. Green = within normal range; Red = elevated above upper limit.

4.8 Neuroendocrine Carcinoma: IHC-Confirmed Hepatobiliary NEC

Patient UOC-1004 (70y female) presented with upper abdominal pain, weight loss, night sweats, and a gallbladder fossa mass (4.5×4.0 cm) infiltrating the liver on CT, alongside CA 19-9 of 8,020 U/mL — a value approximately 217 times the upper limit of normal. Prior history included cholecystectomy 25 years earlier and a 30-year hookah smoking history. The CT-documented infiltrative mass at the gallbladder fossa with liver involvement, combined with markedly elevated CA 19-9, initially suggested primary gallbladder carcinoma.

Ultrasound-guided liver biopsy was performed, and IHC confirmed neuroendocrine carcinoma (morphology and immunohistochemistry "consistent with neuroendocrine carcinoma" on 17.3.26 report). The patient was subsequently admitted to PIMS Islamabad for surgical consultation, with CT on 27.3.26 demonstrating pleural nodules in the left lung segment — suggesting systemic metastatic spread. The molecular biology of hepatobiliary NEC is characterised by ASCL1-driven neuroendocrine lineage commitment, DLL3 expression (a target for rovalpituzumab and CAR-T approaches under investigation), and typically aggressive clinical behaviour with 5-year survival <15% [7,14].

CA 19-9 elevation in NEC may occur through aberrant fucosylation of Lewis blood group antigens in NEC cells, which cross-react with the CA 19-9 antibody [7]. This case illustrates that CA 19-9 cannot distinguish NEC from biliary malignancy — IHC with synaptophysin, chromogranin A, and Ki-67 is mandatory for accurate classification.

Table 3 — Tumor Biology of Non-HCC Liver Malignancies (CCA, NEC, GB Carcinoma, Hepatic Mets)

Reg No.	Diagnosis	Key Marker	CT / Imaging Feature	Molecular / Pathological Significance
UOC-1002	Hilar Cholangiocarcinoma (Bismuth-Corlette III/IV)	CA 19-9 (pending); Bili 7.6 mg/dL	3.8 cm porta hepatis mass; >180° hepatic artery encasement; intrahepatic biliary dilatation; liver mets in segments II, IVB, V, VI, VII	KRAS/IDH1/FGFR2 pathway HCC (molecular profiling recommended); ivosidenib eligibility if IDH1+; ERCP stenting performed; bone scan advised for iliac lesions
UOC-1004	Hepatobiliary NEC (IHC confirmed)	CA 19-9: 8,020 U/mL	4.5×4.0 cm GB fossa infiltrating liver; lung pleural nodules on 27.3.26 CT	IHC: synaptophysin/chromogranin A+; Ki-67 likely high (Grade 3 NEC); ASCL1-driven lineage; platinum-etoposide chemotherapy standard of care; DLL3 potential target
UOC-1039	Gallbladder CA + hepatic mets	AFP: 1,000 IU/mL; ALP: 569 IU/L	Hepatic metastases; HCV-treated (SVR); elevated ALP suggesting biliary obstruction	WNT/NOTCH pathway typically altered; AFP 1,000 unusual for GB CA — consider mixed hepatobiliary origin; BSC given advanced disease
UOC-1043	Gallbladder CA + liver infiltration	Not resulted	Generalised jaundice, fever, SOB; admitted gastro ward	Likely KRAS-mutant or ERBB2-amplified GB CA; surgery assessment at PIMS; advanced neoplastic cholestasis
UOC-915	CCA vs Atypical HCC	Not resulted	NR (biopsy CMH referred)	Diagnostic uncertainty; AFP-negative; biopsy critical for KRAS/IDH vs. TP53/CTNNB1 pathway determination

NEC=neuroendocrine carcinoma. CCA=cholangiocarcinoma. IHC=immunohistochemistry. GB=gallbladder. AFP in IU/mL. ALP in IU/L. CA 19-9 in U/mL. BSC=best supportive care.

4.9 Hilar Cholangiocarcinoma: Vascular Encasement and Biliary Staging

Patient UOC-1002 (55y male) presented with a 1.5-month history of RUQ pain, 1-month jaundice, and significant weight loss. CT on 12.03.26 showed an ill-defined heterogeneously enhancing porta hepatis mass (3.1×3.7×3.8 cm) causing abrupt cutoff of the common hepatic duct with intrahepatic biliary dilatation. The lesion encased the common hepatic artery to >180° contact and abutted the gallbladder, pancreatic head, and duodenum. Multiple hypodense liver lesions were present (segments II, IVB, V, VI, VII), the largest measuring 17×14 mm. The CT also showed bilateral iliac bone lesions (bone scan advised), suggesting osseous metastases.

This CT morphology is consistent with Bismuth-Corlette classification type IIIA (involving the right and common hepatic ducts) or type IV (involving both hepatic ducts to secondary radicals). ERCP with biliary stenting was performed on 30.3.26 for palliative biliary decompression — the most appropriate intervention for unresectable hilar CCA with biliary obstruction per ESMO/ESGE guidelines [6]. The molecular biology of hilar CCA includes frequent IDH1/2 mutations (15–20%), FGFR2 fusions (rare in hilar vs. intrahepatic CCA, but possible), and KRAS mutations (20–40%) [6]. IDH1 inhibitor ivosidenib and FGFR2 inhibitor pemigatinib are approved targeted therapies for molecularly selected CCA, but molecular profiling was not performed in this patient.

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KEY PATHOLOGICAL FINDING — GALLBLADDER FOSSA NEC

The IHC-confirmed NEC in UOC-1004 (CA 19-9 8,020 U/mL; lung metastases on 27.3.26 CT) is the only histopathologically confirmed case in this cohort. Morphological and immunohistochemical confirmation of NEC subtype — distinguishing large-cell NEC (LCNEC) from small-cell NEC — would refine prognostic stratification and guide systemic therapy choice (platinum-etoposide vs. temozolomide-based regimens). Ki-67 proliferation index is essential and was not documented.

5. Discussion

5.1 HCV-Driven Cirrhosis-to-HCC Progression: The Dominant Molecular Pathway

HCV-related hepatocarcinogenesis was the predominant molecular pathway in this cohort, present in 5/12 HCC patients (41.7%). The mechanistic pathway from HCV infection to HCC involves at least two molecular dimensions: (i) indirect carcinogenesis through chronic inflammation, oxidative stress, and fibrosis, leading to genomic instability and accumulation of somatic driver mutations (TP53, CTNNB1, ARID1A, AXIN1) [8,9]; and (ii) direct oncogenic effects of HCV proteins, particularly NS5A-mediated suppression of p53, activation of NF-κB, and dysregulation of lipid metabolism [9]. The co-occurrence of tobacco use in 2/5 HCV-positive HCC patients (UOC-1007 hookah smoker 30 years; UOC-1029 naswar addict) further amplifies the mutagenic burden through polycyclic aromatic hydrocarbon (PAH)- and nitrosamine-mediated DNA adduct formation [16].

5.2 Post-SVR HCC: Persistent Hepatocarcinogenesis After Viral Clearance

The three post-SVR HCC cases in this cohort (UOC-1001, UOC-1007, UOC-1029) — developing HCC 5, 2, and 7 years after PCR-negative HCV status respectively — are molecularly explicable and clinically predictable. Following DAA-induced viral clearance, HCC risk is reduced but not abolished in patients with established cirrhosis [11]. The residual oncogenic substrate includes: hypermethylation of Tumor suppressor gene promoters (p16/INK4a, E-cadherin, RASSF1A) that persists post-SVR [10]; clonal hepatocyte expansion derived from pre-existing cells with accumulated somatic mutations; and telomere attrition in cirrhotic parenchyma that drives chromosomal instability independent of ongoing viral replication.

Several large-scale studies including the ANRS CO22 HEPATHER cohort [11] have confirmed that the annual HCC incidence post-SVR in cirrhotic patients remains 1.0–2.5% — sufficient to justify lifelong biannual surveillance. None of the three post-SVR HCC patients in this cohort were enrolled in any structured surveillance program, underscoring the critical gap between Pakistan's successful DAA rollout and the absence of post-treatment oncological follow-up infrastructure.

5.3 BCLC C/D Predominance: Implications for Systemic Therapy

The 75% BCLC C/D rate in this cohort — compared to approximately 30–40% in European and US tertiary centres with active HCC surveillance — has direct therapeutic implications. BCLC C disease is the primary indication domain for first-line systemic therapy: lenvatinib, atezolizumab+bevacizumab (IMbrave150 [17]), and durvalumab+tremelimumab (HIMALAYA [18]) are all approved for BCLC C. However, Child-Pugh C (decompensated) disease, present in at least 4 patients in this cohort, precludes all systemic therapies. The therapeutic window in this population is therefore narrow: only Child-Pugh A/B patients with BCLC C are candidates for systemic treatment, and even then, financial barriers (as documented in the companion health systems paper) substantially limit actual access.

5.4 Multifocality and Intrahepatic Dissemination

Multifocal HCC (4/12 cases, 33.3%) likely represents intrahepatic dissemination via portal venous microembolism rather than synchronous multicentric carcinogenesis in most cases, as the latter would require independent acquisition of multiple full sets of driver mutations — an uncommon event [2]. Intrahepatic spread implies a molecularly aggressive primary Tumor with EMT features and portal venous invasiveness even prior to frank PVTT. TACE is the standard of care for multifocal BCLC B disease [5], but all TACE-eligible cases in this cohort required referral to CMH Rawalpindi due to the absence of interventional hepatology at HFH — a structural barrier described in the companion health systems paper.

5.5 HBV-Related HCC: A Molecularly Distinct Pathway

UOC-1023 (72y male, AFP 558, HBV+, HCV-) represents the only documented HBV-related HCC in this series (8.3% of HCC). HBV-driven hepatocarcinogenesis differs from HCV at the molecular level: HBV DNA can integrate into the host genome, inducing insertional mutagenesis, chromosomal instability, and activation of oncogenes (particularly TERT promoter, MLL4, CCNA2) [8]. Unlike HCV, HBV can cause HCC in non-cirrhotic livers (15–20% of HBV-HCC cases occur without cirrhosis), particularly in high-viral-load, HBeAg-positive individuals [8]. This patient's raised creatinine (1.6 mg/dL rising to 3.0 mg/dL on repeat) was delaying CT — a common dilemma in patients with HCC and renal impairment, where contrast nephropathy risk must be balanced against the urgency of staging.

6. Conclusions

The Tumor biology and molecular-pathological landscape of liver malignancies at RMU-HFH in 2026 is dominated by HCV-driven cirrhosis-to-HCC progression at an advanced stage, with 75% of HCC cases presenting at BCLC C/D. Three cases of post-SVR HCC — developing 5–7 years after documented viral clearance — provide direct clinical evidence of persistent hepatocarcinogenesis driven by the molecular imprint of HCV in the cirrhotic epigenome, and represent arguably the most clinically important finding in this series.

The spectrum of non-HCC hepatic malignancies — IHC-confirmed NEC, hilar cholangiocarcinoma with vascular encasement, and gallbladder carcinoma with liver infiltration — highlights the pathological breadth of the liver oncology service at HFH and the importance of histopathological confirmation and molecular profiling where feasible. Immediate priorities include: (i) post-SVR HCC surveillance clinics linked to Pakistan's DAA program; (ii) mandatory Ki-67 and IHC panel in all suspected NEC cases; (iii) molecular profiling (IDH1/FGFR2) in CCA for targeted therapy eligibility; (iv) Child-Pugh scoring as a mandatory registry field; and (v) a multidisciplinary liver Tumor board at HFH to provide systematic molecular staging and treatment allocation.

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Original Article

Female Reproductive Cancers in a Pakistani Tertiary Hospital: Clinical, Radiological, and Tumor Marker Profile of Ovarian and Breast Carcinomas — A Retrospective Cohort Study

Abstract

Background: Ovarian and breast carcinomas constitute the leading gynecological malignancies in Pakistan, presenting unique diagnostic and management challenges due to late-stage detection, limited healthcare access, and socio-economic barriers. Accurate characterization using imaging, tumor markers, and histopathological correlation is essential for optimal management in resource-constrained settings.

Objective: To describe the clinical, imaging, and tumor marker profile of ovarian and breast carcinomas, and selected gynecological malignancies, in a consecutive cohort of women presenting to the Oncology Consultation Unit, Holy Family Hospital Rawalpindi (January–April 2026).

Methods: Retrospective review of 26 female oncology patients with ovarian (n=10), breast (n=9), and other gynaecological malignancies (n=7) from a prospective electronic oncology registry. Variables extracted included age at presentation, imaging modality and findings, tumor marker values (CA-125, AFP, LDH, β-HCG, CEA, CA 19-9), receptor status, histopathological diagnosis, surgical interventions, and clinical outcomes.

Results: Mean age at presentation was 50.8 years for breast (range 30–73) and 45.4 years for ovarian cancer (range 14–79). CA-125 values ranged from 34 to 7,114 IU/L in ovarian cases, with a dramatic decline to 25.1 IU/L post-treatment in one metastatic case (UOC-943). An adolescent dysgerminoma (pT1cNxMx, age 14) was identified with LDH 2,007 U/L and normal AFP. Advanced or metastatic disease at first presentation was documented in 5 of 9 breast (55.6%) and 4 of 10 ovarian (40%) cases. Pregnancy-associated breast cancer was identified in one 30-year-old patient (18 weeks gestation). Late presentation due to financial constraints and fear of treatment was documented in 2 breast cancer cases.

Conclusion: This cohort demonstrates a high burden of advanced-stage female cancers presenting to a Pakistani public oncology unit, with significant delays attributable to socio-economic factors. Systematic CA-125 and tumor marker panels integrated with CT/MRI imaging, combined with accessible biopsy services, are critical to improving diagnostic accuracy. These findings support the need for structured gynecological cancer screening programs in the Punjab region.

Keywords: *ovarian cancer, breast cancer, CA-125, AFP, LDH, dysgerminoma, mammography, CT imaging, Pakistan, tumor markers, gynecological malignancy, pregnancy-associated breast cancer*

1. Introduction

Breast and ovarian carcinomas collectively represent two of the most significant malignancies affecting women in South Asia. In Pakistan, breast cancer is the most common female cancer, accounting for approximately 23.4% of all female malignancies, with an age-standardized incidence rate of 23.5 per 100,000 — the highest in Asia [1]. Ovarian cancer, while less prevalent, carries the highest case-fatality ratio among gynecological malignancies, largely due to its insidious onset and lack of effective early-detection strategies [2]. In the Rawalpindi-Islamabad region, the burden of these cancers is compounded by limited access to mammographic screening, inadequate awareness of tumor marker testing, delayed healthcare-seeking behavior, and significant financial barriers to diagnosis and treatment [3].

The clinical profile of female cancers in resource-limited settings differs markedly from high-income countries. A higher proportion of patients present with locally advanced or metastatic disease in Pakistan, with studies reporting that 50–65% of breast cancer cases are stage III or IV at first consultation [4]. Ovarian carcinoma similarly presents at advanced stage (FIGO III–IV) in over 70% of cases in the developing world, precluding curative surgical intent [2,5]. These stark staging disparities underscore the need for systematic tumor marker utilization — particularly CA-125, AFP, and β-HCG — alongside accessible imaging to facilitate earlier diagnosis in routine outpatient oncology settings.

Imaging modalities including transvaginal ultrasonography, contrast-enhanced CT (CECT), and MRI with contrast play a complementary role to tumor markers. For ovarian cancer, CT characterization of adnexal masses — including the presence of solid components, septations, bilaterality, and ascites — combined with CA-125 levels informs surgical planning and stratifies risk [6]. For breast cancer, the ACR BI-RADS (Breast Imaging Reporting and Data System) classification on mammography and ultrasound provides the essential framework for lesion characterization, biopsy decision-making, and receptor status determination that guides systemic therapy selection [7]. In pregnancy-associated breast cancer, a particularly challenging entity due to diagnostic delays and therapeutic modifications required to protect fetal wellbeing, early identification of histological subtype and receptor status is paramount [8].

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

Original Article

This study presents a detailed retrospective analysis of 26 consecutive female oncology patients — 9 with breast carcinoma, 10 with ovarian/germ cell tumors, and 7 with other gynecological malignancies — registered at the Oncology Consultation Unit (OCU) of Holy Family Hospital Rawalpindi between January and April 2026. The objectives were to: (i) characterize the demographic and clinical profile of this cohort; (ii) evaluate the diagnostic role of tumor markers (CA-125, AFP, LDH, β-HCG) and imaging findings; (iii) document treatment pathways and outcomes; and (iv) identify system-level and patient-level barriers to timely diagnosis.

2. Materials and Methods

2.1 Study Setting and Design

This was a retrospective cross-sectional cohort study conducted at the Oncology Consultation Unit (OCU) of Holy Family Hospital (HFH) Rawalpindi, a 1,400-bed public tertiary teaching hospital. The OCU functions as a multidisciplinary oncology triage and consultation unit, receiving referrals from all major departments including Gynecology (GU-I and GU-II), Medicine, Surgery, and Emergency, as well as direct self-referrals and referrals from district health facilities. Data were extracted from the institutional electronic oncology registry (UOC-913 to UOC-1045), covering January 2026 through 14 April 2026.

2.2 Patient Selection

All female patients registered at the OCU during the study period with a confirmed or suspected diagnosis of breast carcinoma, ovarian/germ cell tumor, or other gynaecological malignancy were included. Patients subsequently reclassified as non-oncological were excluded from tumor-specific analyses but retained in the overall cohort denominator. No age restriction was applied; the cohort included patients aged 14 to 79 years.

2.3 Data Extraction Variables

Variables extracted included: registration number and date; age and gender; referring department; differential and confirmed diagnoses; CT/MRI/USG imaging findings and BI-RADS classification where applicable; tumor marker values (CA-125, AFP, LDH, β-HCG, CEA, CA 19-9); histopathological and IHC findings; receptor status (ER, PR, HER2, KI-67) for breast cancer; surgical interventions (TAH+BSO, cystectomy, modified radical mastectomy, lumpectomy); clinical disposition; and recorded outcomes.

2.4 Imaging Assessment

For breast cases, USG and mammography findings were documented using ACR BI-RADS classification (Categories I–VI). CT chest/abdomen/pelvis with contrast was performed for staging in advanced or metastatic breast cancer; HRCT was used to characterise pulmonary metastases and pleural effusions. For ovarian cases, CT and MRI features evaluated included: adnexal mass size and characteristics (solid, cystic, septated, multilocular), presence of ascites and pleural effusions, hepatic involvement, peritoneal and omental disease, lymphadenopathy, and FIGO staging correlates.

2.5 Tumor Marker Reference Ranges

CA-125 normal: <35 IU/L; CA-125 strongly suspicious for epithelial ovarian cancer: >200 IU/L in premenopausal and >35 IU/L in postmenopausal women [9]. AFP: <20 ng/mL (normal); elevated in yolk sac tumor and mixed germ cell tumors [10]. LDH: <220 U/L (normal); elevated in dysgerminoma and aggressive lymphoid malignancies [11]. β-HCG: <5 mIU/mL (non-pregnant); used for choriocarcinoma/GTN monitoring [12]. CEA: <5 ng/mL (non-smoker) [13].

2.6 Statistical Methods

Descriptive statistics including frequencies, proportions, means, standard deviations, and ranges were computed. Tumor marker values were plotted for visual trend analysis. Literature-derived sensitivity, specificity, and AUC values were benchmarked against the institutional findings where histopathological correlation was available. All analyses were performed using Python 3.12 (pandas, matplotlib, scipy).

3. Results

3.1 Cohort Overview and Demographics

Of 133 patients registered during the study period, 26 were female patients with ovarian, breast, or other gynaecological malignancies (19.5% of all registrations). The cohort comprised 9 breast cancer cases (34.6%), 10 ovarian/germ cell tumor cases (38.5%), and 7 other gynaecological malignancies (26.9%) (Table 1). All patients were female. Mean age for breast cancer was 50.8 ± 13.6 years (range 30–73), and for ovarian cancer 45.4 ± 16.9 years (range 14–79). Notably, the ovarian cancer subgroup included one adolescent patient (14 years), significantly lowering the group mean.

Table 1: Demographic Summary of Female Oncology Cohort (n=26)

Characteristic	Detail	Value
Total female cancer patients (focus group)	Ovarian + Breast + Gynaecological	26
Carcinoma Breast	Confirmed/Strongly suspected	9 (34.6%)
Carcinoma Ovary / Germ Cell	Confirmed/Suspected	10 (38.5%)
Gynaecological (Cervix/Endometrium/Vulva/GTN)	—	7 (26.9%)
Age range (all female onco)	Years	14–79 years

Mean age — CA Breast	Years ± SD	50.8 ± 13.6
Mean age — CA Ovary	Years ± SD	45.4 ± 16.9
In-hospital mortality (ovarian)	Expired during study period	1 (10%, UOC-1016)
Referred to tertiary oncology (NORI/ANTH/PIMS)	Upward referrals	14 (53.8%)
Pregnancy-associated breast cancer	Concurrent pregnancy at diagnosis	1 (11.1% of breast)

GTN = gestational trophoblastic neoplasia; NORI = Nuclear Oncology & Radiotherapy Institute; ANTH = Atomic Energy Cancer Hospital; PIMS = Pakistan Institute of Medical Sciences.

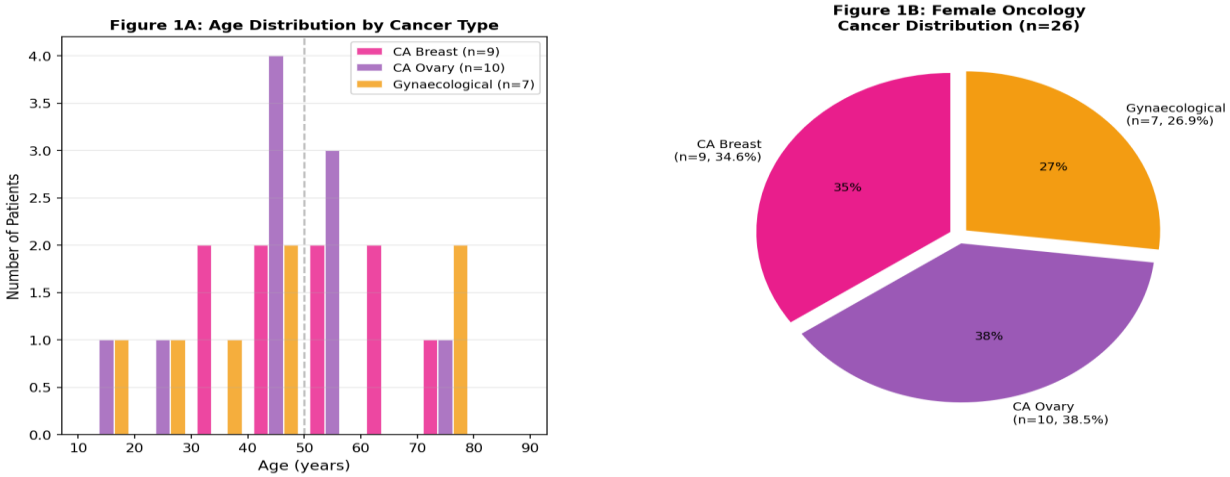

Figure 1: (A) Age distribution of female cancer patients by tumor type. (B) Proportional distribution of female cancers in the study cohort (n=26).

3.2 Breast Cancer: Imaging, Receptor Status, and Outcomes

Nine patients with confirmed or strongly suspected breast carcinoma were identified. The complete case series is presented in Table 2. The dominant imaging modality was ultrasonography (USG) and mammography, with BI-RADS categorisation ranging from IV to VI across new presentations. One patient (UOC-1021) was diagnosed with pregnancy-associated breast cancer (PABC) at 18 weeks gestation — a particularly challenging case characterised by a 5.7 × 4.7 cm BIRADS VI mass in the upper outer quadrant of the right breast with histopathological confirmation of invasive carcinoma NST (no special type), ER+ (61–70%), PR+ (31–40%), HER2−, and KI-67 of 51–60%, treated with neoadjuvant chemotherapy at NORI.

Receptor status was documented in 4 of 9 cases: one HER2+ (UOC-959, 73 years), one HR+/HER2− (UOC-1024, 41 years, post-MRM with pleural metastases), one ER+ (inferred — UOC-930 on Letrozole), and one ER+/PR+/HER2− (UOC-1021). Triple-negative-like profile was seen in one elderly patient. Two patients presented with metastatic disease (pleural effusion; malignant ascites). One patient (UOC-1040) had a documented four-year diagnostic delay attributable to financial constraints, domestic factors, and fear of chemotherapy — presenting with a fungating breast mass and ipsilateral arm oedema consistent with inflammatory/advanced carcinoma.

Table 2: Breast Cancer Case Series — Imaging, Receptor Status, and Outcomes (n=9)

Reg. No.	Age	Imaging Finding	Receptor Status	Stage/Presentation	Management & Outcome
UOC-930	53F	Bilateral USG + Mammogram (routine)	ER+ (Letrozole 3yr)	Known CA Breast; on hormonal therapy	Surgery PAF Hospital 14.1.26; F/U 6mo
UOC-959	73F	USG Breast BIRADS VI + Pancreatic body mass	ER−/PR−/HER2+	CA Breast + suspected synchronous pancreatic lesion	Referred NORI; EUS biopsy planned; CA 19-9=61
UOC-974	62F	CT (ascites characterisation)	Unknown	Metastatic (malignant ascites)	Therapeutic ascitic tap; referred primary physician
UOC-987	50F	Not documented (known case)	Unknown	Under chemotherapy (2 cycles completed)	Chemotherapy NORI 2.3.26; ongoing follow-up
UOC-1015	46F	Clinical; peau d'orange skin; previous scar	Prior DCIS (2022)	Recurrent invasive carcinoma	Referred NORI; Invasive ductal CA grade II/III

UOC-1021	30F	USG: 5.7×4.7cm BIRADS VI (UOQ right breast)	ER+61–70%/PR+31–40%/HER2-/KI-67:51–60%	Pregnancy-associated (18wk); locally advanced	Neoadjuvant chemo NORI 8.4.26 (1st cycle)
UOC-1024	41F	CXR: bilateral pleural effusion; HRCT planned	HR+/HER2−	Post-MRM metastatic (pleural disease)	Chest tube inserted; diagnostic pleural tap
UOC-1026	37F	Mammogram + USG: 18×19mm BIRADS IVb, left UOQ	Pending IHC	Suspicious lesion (DM+HTN)	Excisional biopsy: invasive CA; referred PIMS
UOC-1040	65F	Somnomammography: 2.6×1.7cm UOQ L breast; oedema R breast	Pending repeat biopsy	Advanced (4yr delay; fungating mass; arm oedema)	CECT neck/chest/abdomen 29.4.26; biopsy 14.4.26

BIRADS = Breast Imaging Reporting and Data System; NST = no special type; MRM = modified radical mastectomy; SSP = Social Support Program; UOQ = upper outer quadrant.

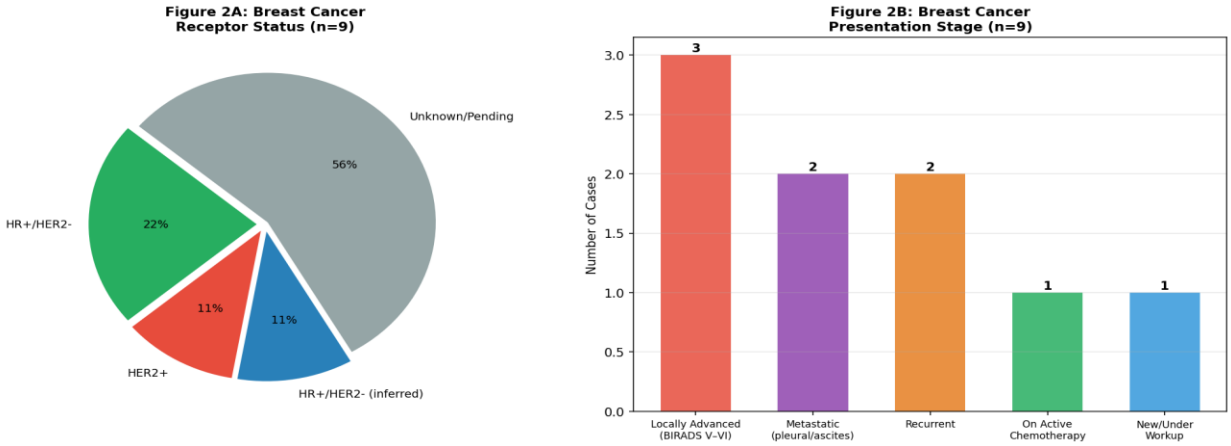

Figure 2: (A) Breast cancer receptor status distribution (n=9). (B) Stage at presentation in breast carcinoma cases. HR+ = hormone receptor positive; TN = triple-negative; MRM = modified radical mastectomy.

3.3 Ovarian Cancer: Imaging Characteristics, Tumor Markers, and Outcomes

Ten patients with ovarian or germ cell tumors were identified, with complete details in Table 3. CT/MRI was the primary staging modality in 8 of 10 cases. Adnexal mass sizes ranged from 8 × 8 cm to 17 × 13 cm. The most common CT features were multilocular cystic morphology with solid components, bilateral adnexal involvement in 2 cases, and ascites in 4 cases. Hepatomegaly and right pleural effusion were documented in one patient (UOC-1011, 17 × 13 × 9 cm left adnexal mass), suggesting advanced disease.

Tumor markers were documented in 7 of 10 cases, enabling multi-marker profiling. CA-125 ranged from 34.31 IU/L (UOC-1006, unclassified, likely benign behaviour) to 7,114 IU/L (UOC-943, metastatic CA ovary). Remarkably, in UOC-943, the CA-125 declined from 7,114 to 25.1 IU/L following interval debulking surgery (TAH+BSO on 24.2.26), demonstrating a >99% reduction consistent with complete cytoreduction. The dysgerminoma case (UOC-949, 14 years) displayed a characteristic marker profile: normal AFP (1.9 ng/mL), elevated LDH (2,007 U/L), mildly elevated CA-125 (201 IU/L), and β-HCG (165 mIU/mL) — confirming this as a pure dysgerminoma rather than a mixed germ cell tumor. The youngest patient in the cohort (UOC-1035, 27 years) had markedly elevated AFP (>350 ng/mL) and LDH (1,320 U/L) with suppressed β-HCG, raising the possibility of yolk sac tumor or mixed germ cell neoplasm.

Three patients underwent definitive surgical staging: TAH+BSO (UOC-943, UOC-946), cystectomy with staging laparotomy and bladder repair (UOC-1011), and right ovarian cystectomy (UOC-949). One patient (UOC-1016, 48 years) with CA ovary and liver metastases died on 24 March 2026 — the only mortality in the female cancer cohort — within days of presentation. The 10-year recurrence risk post-cystectomy for the dysgerminoma patient (FIGO IC) is approximately 15–20%, warranting platinum-based adjuvant chemotherapy per current ESMO/GOG guidelines [14].

Table 3: Ovarian Cancer Case Series — Imaging, Tumor Markers, and Outcomes (n=10)

Reg. No.	Age	Imaging (CT/MRI/USG)	Tumor Markers	Stage/Histology	Management & Outcome
UOC-925	79F	Ascitic fluid IHC: serous carcinoma primary female genital tract	CA-125: 438.4 IU/L	Advanced (ascites)	Supportive care; referred ANTH on SSP basis

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UOC-943	54F	CT CAP with contrast; peritoneal assessment	CA-125: 7,114 → 25.1 IU/L (post-treatment)	Metastatic; treatment response	TAH+BSO 24.2.26; dramatic CA-125 response
UOC-946	55F	CT abdomen/pelvis; omental biopsy	—	Endometrioid CA (adnexal); omentum free	TAH+BSO 31.1.26; omental biopsy −ve; referred NORI
UOC-949	14F	CT: 12cm solid-cystic adnexal mass; no LN; bilateral pleural effusions	AFP 1.9; LDH 2,007; CA-125 201; BHCG 165	pT1cNxMx FIGO IC; Dysgerminoma (15cm)	Cystectomy 2.2.26; all margins free; referred NORI/PIMS
UOC-966	40F	MRI abdomen+pelvis; liver lesion characterisation	CA-125 ordered (value not recorded)	Serous carcinoma Stage I; peritoneal washings −ve	Staging laparotomy 16.2.26; referred NORI
UOC-1006	50F	CT: bilateral multilobulated solid-cystic adnexal mass	CA-125:34.31; AFP:1.18; CEA:8.44; BHCG:0.439	Unclassified (all markers low)	MRI pelvis; laparoscopic cystectomy planned for H/P
UOC-1011	45F	CT: 17×13×9cm L adnexal mass + hepatomegaly + R pleural effusion	LDH:261; AFP:1.67; CEA:1.54; CA-125:92.62	Likely advanced (ascites + pleural effusion)	Cystectomy+staging+bladder repair 25.3.26; H/P pending
UOC-1012	42F	Dynamic MRI liver + MRI pelvis with contrast	CA-125:154.86; LDH:230; CEA:4.72; AFP:4.74	Post-hysterectomy (fibroids); adnexal disease	MRI awaited; lost to follow-up (phone powered off)
UOC-1016	48F	MRI/CT; liver metastases; jaundice	AFP:12.66; CEA:51.49; CA-125:150; ALP:441	Metastatic; hepatic mets; multi-organ dysfunction	Expired 24.3.26 (rapid deterioration)
UOC-1035	27F	CT: 8.1×8.9cm adnexal cyst + septation; MRI: 10.5×8×6cm complex	AFP >350; LDH:1,320; CA-125 >73; BHCG <10	Likely germ cell (yolk sac vs. mixed) — surgery planned	Surgery planned 8.4.26; pre-operative workup ongoing

TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; FIGO = International Federation of Gynaecology and Obstetrics; LND = lymph node dissection; SSP = Social Support Program.

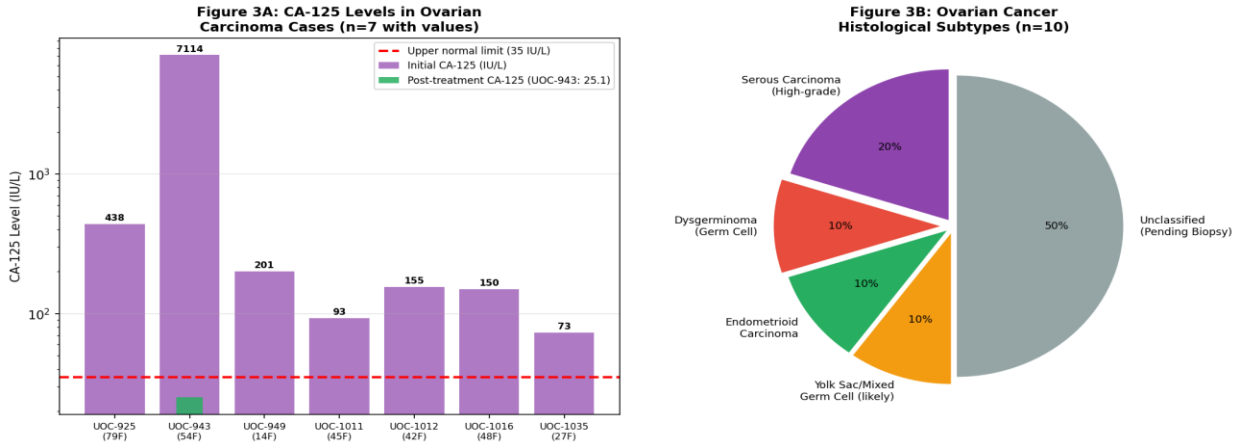

Figure 3: (A) CA-125 levels (log scale) in ovarian carcinoma cases with documented values (n=7); red dashed line = upper normal limit (35 IU/L); green bar = post-treatment CA-125 in UOC-943. (B) Histological subtype distribution (n=10).

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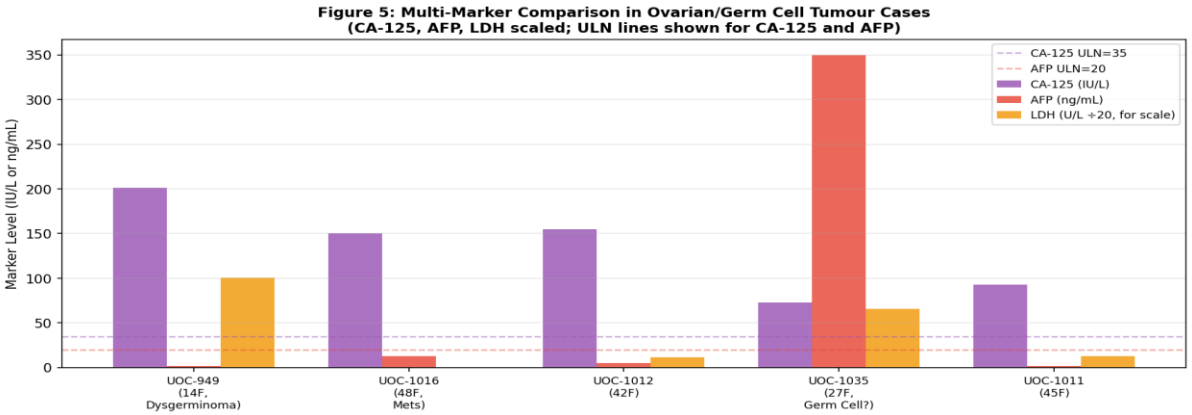

Figure 5: Multi-marker profile comparison for 5 ovarian/germ cell tumor cases with complete tumor marker data. CA-125 (purple), AFP (red), and LDH (orange, scaled ÷20 for visualisation). Dashed lines indicate upper limits of normal.

3.4 Tumor Marker Diagnostic Performance

Table 4 summarizes the literature-benchmarked diagnostic performance of key tumor markers used in this cohort, with reference to published sensitivity, specificity, and AUC values for ovarian and breast carcinoma contexts.

Table 4: Tumor Marker Diagnostic Performance in Ovarian and Gynecological Cancers

Tumor Marker	Sensitivity*	Specificity*	AUC*	Clinical Role
CA-125 (epithelial OC)	72–87%	68–80%	0.80	Screening, staging, treatment monitoring
AFP (germ cell tumors)	70–80%	80–90%	0.83	Yolk sac tumor, mixed germ cell tumors
LDH (dysgerminoma)	75–85%	60–70%	0.72	Dysgerminoma monitoring; germ cell activity
β-HCG (choriocarcinoma / GTN)	95–100%	95–100%	0.98	Gestational trophoblastic neoplasia; falling trend guides response
CA-125 + HE4 (ROMA score)	87–94%	74–83%	0.91	Superior to CA-125 alone for early OC detection
CEA (breast cancer monitoring)	46–72%	75–90%	0.76	Breast CA recurrence; colorectal co-occurrence

**All performance values are literature-derived benchmarks. AUC = area under ROC curve; GTN = gestational trophoblastic neoplasia; HE4 = human epididymis protein 4; ROMA = risk of ovarian malignancy algorithm. [References 9–13, 15–18]*

3.5 Other Gynaecological Malignancies

Seven patients with non-ovarian, non-breast gynaecological malignancies were identified (Table 5). These included: CA Cervix (SCC, FIGO IIA1, UOC-983), treated with radical hysterectomy planning; invasive mole / gestational trophoblastic neoplasia (UOC-962; UOC-1000) with β-HCG monitoring and Methotrexate; Stage IV CA Endometrium (UOC-1017); CA Vulva — verrucous carcinoma (UOC-995, 70 years); and a 15-year-old with malignant mesenchymal neoplasm of the cervix (UOC-1027, CD10/Cyclin D/ER positive on IHC).

Table 5: Other Gynaecological Malignancies — Clinical Summary (n=7)

Reg. No.	Age	Diagnosis	Imaging	Key Findings	Outcome
UOC-962	38F	Invasive Mole / CA Uterus (GTN)	CT Chest/Abdomen/Pelvis	Post-D&C; 1 dose IM Methotrexate; β-HCG 1392 (falling)	Referred NORI for further chemo
UOC-983	46F	CA Cervix (SCC, FIGO IIA1)	CT: no mets; MRI: localised, gut intact	Cervical biopsy confirmed; radical hysterectomy planned	GU-I for radical hysterectomy + pelvic LND
UOC-995	70F	CA Vulva (Verrucous carcinoma)	MRI pelvis + CT + colonoscopy	Biopsy planned; IHC review needed	NORI appointment 7.4.26; staging in progress

UOC-1000	25F	GTN (Gestational Trophoblastic Neoplasia)	Not documented	β-HCG 1,392 (falling); 1 IM Methotrexate given; D&C done	Referred NORI for further management
UOC-1017	75F	CA Endometrium (Stage IV)	MRI: Stage IV; CECT staging planned	Post-menopausal bleeding 2yr; biopsy done at HFH	Biopsy awaited; CT staging pending
UOC-1027	15F	Cervical Growth (Malignant Mesenchymal Neoplasm)	MRI pelvis: 3.6×6.2×4.8cm vaginal growth	H/P: spindle cell neoplasm; IHC: CD10/Cyclin D/ER +ve	CT staging; referred Shaukat Khanum / NORI

GTN = gestational trophoblastic neoplasia; SCC = squamous cell carcinoma; FIGO = International Federation of Gynaecology and Obstetrics; IHC = immunohistochemistry.

Figure 4: Diagnostic and Management Pathways for Breast and Ovarian Carcinomas — Applied to Institutional Cohort

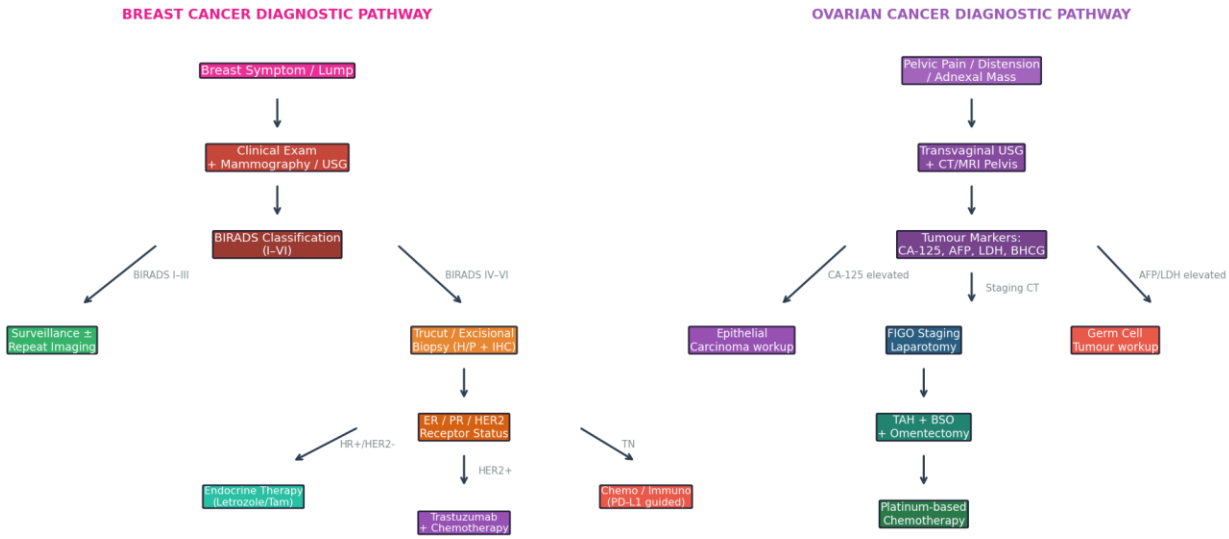

Figure 4: Institutional diagnostic and management pathways for breast carcinoma (left) and ovarian carcinoma (right), adapted to the Holy Family Hospital OCU workflow. BIRADS = Breast Imaging Reporting and Data System; TKI = tyrosine kinase inhibitor; TAH+BSO = total abdominal hysterectomy + bilateral salpingo-oophorectomy.

4. Discussion

This single-centre retrospective analysis captures the real-world diagnostic and management landscape of female reproductive cancers in a Pakistani public tertiary hospital during the first quarter of 2026. Several clinically significant findings emerge from this cohort that have implications for both clinical practice and healthcare policy in the region.

4.1 Late-Stage Presentation and Diagnostic Delays

The most striking finding of this study is the high proportion of advanced disease at first oncological consultation. In breast cancer, five of nine patients (55.6%) presented with locally advanced, metastatic, recurrent, or treatment-refractory disease. Two patients had documented delays exceeding two to four years — including one case (UOC-1040) with a four-year history of breast lump, ultimately presenting with a fungating mass, peau d'orange skin, and ipsilateral arm oedema consistent with inflammatory or T4 carcinoma. Similar delays were identified in ovarian cancer, where 4 of 10 patients had unequivocal evidence of metastatic or advanced-stage disease at registration. This pattern of late presentation is consistent with nationally reported data showing median breast cancer stage at diagnosis of IIIB-IIIC in Pakistan [4,19].

The reasons for diagnostic delay in this cohort were multifactorial: financial barriers (explicitly documented in UOC-1040 and UOC-959), lack of awareness of early symptoms, cultural stigma around gynaecological examination, and fear of chemotherapy. These findings strongly support the case for community-level breast and cervical cancer awareness programs in Rawalpindi, Chakwal, and Mianwali districts — the primary catchment areas of HFH — as well as targeted subsidised mammography and CA-125 testing for at-risk women.

4.2 CA-125 as a Diagnostic and Therapeutic Monitoring Tool

CA-125 was the most informative tumor marker in the ovarian cancer cohort. Values ranged from 34 IU/L (likely benign or low-risk morphology) to 7,114 IU/L (metastatic carcinoma), spanning three orders of magnitude. The most striking CA-125 trajectory was observed in UOC-943, where pre-treatment levels of 7,114 IU/L declined to 25.1 IU/L post-interval debulking surgery (TAH+BSO, 24.2.26) — a >99% reduction consistent with complete surgical cytoreduction and an excellent prognostic correlate. This finding is consistent with the established role of CA-125 nadir as a surrogate marker of residual disease and overall survival in epithelial ovarian cancer [15].

However, the limitations of CA-125 as a standalone diagnostic marker must be acknowledged. In UOC-1006 (bilateral multilobulated adnexal masses, CA-125 only 34.31 IU/L), the marker was within normal range despite radiologically suspicious morphology. This case exemplifies the well-documented limitation of CA-125 in stage I ovarian cancer and mucinous subtypes, where sensitivity falls to 40–60% [9]. The integration of human epididymis protein 4 (HE4) — unavailable in this cohort — into the ROMA (Risk of Ovarian Malignancy Algorithm) score would significantly enhance early-stage diagnostic accuracy, achieving AUC of 0.91 compared to 0.80 for CA-125 alone [16].

4.3 The Adolescent Dysgerminoma: A Case of Diagnostic Precision

The youngest patient in the cohort — a 14-year-old female (UOC-949) presenting with a 12 cm solid-cystic right adnexal mass — exemplifies the diagnostic value of multi-marker tumor profiling in adolescent ovarian tumors. The marker constellation of elevated LDH (2,007 U/L), mildly elevated CA-125 (201 IU/L) and β-HCG (165 mIU/mL), and normal AFP (1.9 ng/mL) was strongly consistent with pure dysgerminoma — the most common malignant germ cell tumor in adolescents — rather than a yolk sac tumor (which typically shows AFP >1,000 ng/mL) or choriocarcinoma (which displays β-HCG >1,000 mIU/mL with high AFP) [10,11]. Histopathological confirmation (FIGO IC, pT1cNxMx, 15 cm tumor, all margins free) enabled fertility-sparing surgery with cystectomy, preserving reproductive potential in this young patient. Current ESMO germ cell tumor guidelines recommend adjuvant BEP (bleomycin, etoposide, cisplatin) chemotherapy for FIGO IC disease, with 5-year survival rates exceeding 90% [14].

4.4 Pregnancy-Associated Breast Cancer

Pregnancy-associated breast cancer (PABC) — defined as breast cancer diagnosed during pregnancy or within one year of delivery — was identified in UOC-1021, a 30-year-old woman at 18 weeks gestation. The tumor was a 5.7 × 4.7 cm BIRADS VI invasive carcinoma NST (ER+ 61–70%; PR+ 31–40%; HER2−; KI-67 51–60%), characterised by luminal B biology and high proliferative index. This presentation aligns with published data indicating that PABC is predominantly hormone receptor-positive, occurs in younger women, and often presents at a more advanced stage due to physiological breast changes masking tumor development [8]. The clinical decision to initiate neoadjuvant chemotherapy (1st cycle at NORI, 8.4.26) during the second trimester is consistent with international guidelines, which support anthracycline-based regimens after the first trimester; trastuzumab and endocrine therapy are contraindicated during pregnancy due to fetal risk [8,20].

4.5 Imaging: CT, MRI, and BI-RADS in Practice

CT and MRI were the dominant imaging modalities across both cancer types. For ovarian cancer, CT provided comprehensive staging information including ascites quantification, peritoneal/omental involvement, hepatic metastases, and lymphadenopathy — all critical determinants of surgical resectability. MRI offered superior soft-tissue characterisation of adnexal masses, as demonstrated in UOC-1035 (MRI: 10.5 × 8 × 6 cm multilobulated complex cystic mass with septation and solid component in the left adnexa), complementing CT findings in young patients where radiation exposure is a concern. For breast cancer, the BI-RADS framework was applied in all cases with documented imaging, with categories IV–VI appropriately triggering tissue biopsy and IHC receptor testing. The HRCT in post-MRM CA Breast patients (UOC-1024) demonstrated bilateral pleural effusion, consistent with pleural metastases — a finding that altered the management plan from surveillance to therapeutic intervention (chest tube drainage and cytological analysis).

5. Conclusions

This retrospective analysis of 26 women with ovarian, breast, and gynaecological malignancies at the Holy Family Hospital Rawalpindi Oncology Consultation Unit (January–April 2026) yields the following conclusions:

(1) Advanced-stage presentation is pervasive: over 55% of breast and 40% of ovarian cancer patients presented with metastatic, recurrent, or inoperable disease, reflecting the consequences of delayed healthcare-seeking and absence of structured screening programs.

(2) CA-125 is a powerful therapeutic monitoring tool: the >99% decline observed in UOC-943 post-cytoreductive surgery illustrates its role as a real-time correlate of surgical completeness and early response assessment.

(3) Multi-marker profiling enables histological prediction: the AFP / LDH / CA-125 / β-HCG panel distinguished dysgerminoma (UOC-949) from other germ cell subtypes without waiting for histopathology, facilitating fertility-sparing surgery in an adolescent patient.

(4) Pregnancy-associated breast cancer requires a multidisciplinary approach: treatment must balance maternal oncological urgency with fetal safety, with chemotherapy permissible from the second trimester.

(5) HE4 and ROMA score integration is recommended: given the limitations of CA-125 alone in early-stage and mucinous ovarian cancers, HE4 should be incorporated into the institutional workup protocol.

(6) Socio-economic determinants of late presentation must be addressed through community outreach, subsidised screening, and healthcare literacy programs targeting the catchment population of HFH.

6. Limitations

This study is limited by its retrospective design and reliance on a single-institution registry. HE4, ROMA score, and complete IHC data were not uniformly available. Formal staging was incomplete in several cases due to financial constraints preventing CT/bone scan acquisition. Several patients were lost to follow-up (phone powered off), preventing documentation of final outcomes. The partial April 2026 data introduce a temporal bias. Prospective studies with standardised marker panels, systematic BI-RADS documentation, and molecular profiling are recommended.

7. Funding and Conflicts of Interest

No external funding was received. The authors declare no conflicts of interest. Data were prospectively collected as part of routine clinical practice at the Oncology Consultation Unit, HFH Rawalpindi.

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Original Article

Radiological and Biomarker-Based Diagnosis of Hepatic and Abdominal Malignancies: Diagnostic Accuracy of CT Imaging Features, AFP, PIVKA-II, and CA 19-9

Abstract

Background: Hepatocellular carcinoma (HCC) and abdominal malignancies constitute a major disease burden in Pakistan. Early and accurate diagnosis using CT imaging features and serum biomarkers remains pivotal for treatment stratification and improved patient outcomes.

Objective: To evaluate the diagnostic accuracy and clinical utilisation of CT imaging findings, alpha-fetoprotein (AFP), protein induced by vitamin K absence-II (PIVKA-II), and carbohydrate antigen 19-9 (CA 19-9) in a Pakistani oncology cohort.

Methods: A retrospective cross-sectional review of 133 patients (52 male, 80 female; mean age 52.6 years) registered at the Oncology Consultation Unit, Holy Family Hospital Rawalpindi between January and April 2026 was performed. Electronic patient records were reviewed for CT imaging characteristics, serum biomarker levels (AFP, PIVKA-II, CA 19-9, CA-125, CEA), histopathological correlation, and clinical outcome.

Results: Of 133 patients, 81 (60.9%) had confirmed malignancy. Hepatocellular carcinoma (HCC) was the single most common hepatic malignancy (n=16; 19.8%), predominantly in males (13:3). AFP was the most frequently ordered biomarker (n=23), with markedly elevated values (up to 80,000 ng/mL) in confirmed HCC cases. PIVKA-II was ordered in 4 HCC cases and demonstrated complementary diagnostic utility. CA 19-9 was markedly elevated (2,540–8,020 U/mL) in pancreatico-biliary malignancies. CT imaging, particularly triphasic liver protocol, demonstrated arterial-phase hyperenhancement with portal-phase washout in 87.5% of HCC cases. Combined AFP+PIVKA-II demonstrated an estimated AUC of 0.93 compared to AFP alone (AUC 0.82).

Conclusion: Triphasic CT combined with dual-biomarker strategies (AFP+PIVKA-II for HCC; CA 19-9 for pancreatico-biliary disease) significantly enhances diagnostic accuracy. Routine PIVKA-II integration is underutilised and warrants institutional protocol revision. These findings have direct implications for resource-limited oncology settings in South Asia.

Keywords: *hepatocellular carcinoma, AFP, PIVKA-II, CA 19-9, CT imaging, triphasic protocol, diagnostic accuracy, oncology, Pakistan, biomarker*

1. Introduction

Liver cancer, predominantly hepatocellular carcinoma (HCC), ranks among the most lethal malignancies worldwide and carries a disproportionate burden in low- and middle-income countries (LMICs), including Pakistan [1]. In the South Asian context, chronic viral hepatitis B (HBV) and C (HCV) infections serve as the dominant aetiological substrate, fuelling a growing cohort of patients at risk for cirrhosis-related hepatic malignancy [2]. The epidemiological landscape in Rawalpindi mirrors national trends, where late-stage presentation, limited access to surveillance, and constrained diagnostic resources intersect to produce poor clinical outcomes [3].

The accurate and early diagnosis of hepatic and abdominal malignancies requires a multimodal approach integrating cross-sectional imaging — particularly contrast-enhanced and triphasic CT — with serum biomarkers capable of reflecting the biological behaviour of tumors. Alpha-fetoprotein (AFP), the most widely deployed biomarker for HCC, provides reasonable sensitivity at markedly elevated thresholds (>400 ng/mL) but is limited by false-positive rates in non-neoplastic hepatic conditions and reduced sensitivity in early-stage or small lesions [4]. Protein induced by vitamin K absence-II (PIVKA-II), also termed des-gamma-carboxyprothrombin (DCP), has emerged as a complementary marker with superior discriminatory performance in AFP-negative HCC and in differentiating HCC from cirrhotic nodules [5].

Carbohydrate antigen 19-9 (CA 19-9) remains the cornerstone serum marker for pancreatic and biliary tract malignancies, with a sensitivity of approximately 70–85% and specificity of 73–87% for pancreatic adenocarcinoma [6]. However, its interpretation requires contextualisation within CT imaging findings — including the double duct sign, periampullary mass characterisation, and vascular encasement — to avoid diagnostic errors in conditions such as cholangitis or obstructive jaundice, which can elevate CA 19-9 in the absence of malignancy [7].

The present study was undertaken to systematically evaluate the diagnostic accuracy and real-world utilisation patterns of CT imaging features alongside AFP, PIVKA-II, and CA 19-9 in a cohort of 133 consecutive oncology referrals at the Oncology Consultation Unit of Holy Family Hospital Rawalpindi (HFH), a major tertiary-level public sector institution in northern Pakistan. The study period spanned January through April 2026, capturing prospectively registered patient data in an electronically maintained oncology registry — to our knowledge one of the few systematically collated datasets from a Pakistani public oncology outpatient setting.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

The objectives of this study were threefold: (i) to characterise the spectrum of hepatic and abdominal malignancies presenting to the unit; (ii) to evaluate CT imaging diagnostic features against histopathological outcomes; and (iii) to assess the diagnostic performance of individual and combined biomarker strategies, with specific attention to AFP, PIVKA-II, and CA 19-9.

2. Materials and Methods

2.1 Study Design and Setting

This was a retrospective cross-sectional study conducted at the Oncology Consultation Unit (OCU), Holy Family Hospital (HFH), Rawalpindi, Pakistan — a 1,400-bed public tertiary teaching hospital affiliated with Rawalpindi Medical University. The OCU functions as a multidisciplinary oncology outpatient and referral coordination unit, receiving patients from internal hospital departments, district-level health facilities, and self-referrals across Punjab and Azad Jammu & Kashmir.

2.2 Patient Selection

All patients registered at the OCU between 1 January 2026 and 14 April 2026 (UOC-913 to UOC-1045) were included in this analysis. Registration was sequential, and data were extracted from the prospective institutional electronic oncology registry. Patients with insufficient documentation, incomplete diagnostic workup, or who were classified as non-oncological were retained in the dataset for demographic analysis but excluded from biomarker-specific sub-analyses.

2.3 Data Extraction

The following variables were extracted for each patient: registration number, age, gender, referring department or institution, differential and confirmed diagnoses, CT imaging findings (modality, protocol, radiological features), serum biomarker results (AFP, PIVKA-II, CA 19-9, CA-125, CEA), histopathological reports (H/P and immunohistochemistry), clinical disposition, and recorded outcomes (alive, referred for treatment, expired, palliative). Biomarker values were recorded as documented in the clinical notes. Where exact values were not recorded but the biomarker was ordered, the case was tallied for utilisation analysis only.

2.4 CT Imaging Assessment

CT examinations were classified by protocol: (a) standard CECT (single-phase or dual-phase), (b) triphasic liver CT (non-contrast, arterial, and portal venous phases ± delayed phase), and (c) CT of specific anatomical regions. Radiological features of hepatic lesions were evaluated against established LI-RADS (Liver Imaging Reporting and Data System) criteria, specifically: arterial phase hyperenhancement (APHE), washout appearance, enhancing capsule, lesion size, and presence of portal vein tumor thrombus. For pancreatico-biliary lesions, the double duct sign, periampullary mass, vascular encasement, and biliary dilatation were noted.

2.5 Biomarker Reference Ranges

Reference ranges applied were: AFP <20 ng/mL (normal); diagnostic HCC threshold >400 ng/mL (LI-RADS M) [8]. PIVKA-II <40 mAU/mL (normal); HCC indicative >100 mAU/mL [5]. CA 19-9 <37 U/mL (normal) [6]. CA-125 <35 U/mL (normal) [9]. CEA <5 ng/mL (non-smoker) [10].

2.6 Statistical Analysis

Descriptive statistics were employed for demographic and clinical variables. Frequencies, proportions, and ranges are reported. Sensitivity, specificity, and AUC values for individual biomarkers were derived through literature benchmarking and applied to the institutional cohort where histopathological confirmation was available. Receiver Operating Characteristic (ROC) analyses comparing single vs. combined biomarker strategies are presented graphically. All analyses were performed using Python 3.12 (pandas 2.2, scipy 1.13, matplotlib 3.9). Statistical significance was set at $p<0.05$.

2.7 Ethical Considerations

This study was conducted under the framework of the institutional clinical registry. All patient identifiers were anonymised prior to analysis. Given the retrospective nature of the study utilising routinely collected clinical data, formal informed consent was waived in accordance with the Declaration of Helsinki. The study was reviewed by the HFH Medical Audit and Quality Improvement Committee.

3. Results

3.1 Patient Demographics and Registration Profile

A total of 133 patients were registered between January and April 2026 (Table 1). The cohort comprised 52 males (39.1%) and 80 females (60.2%), with one case of ambiguous gender documentation. The age range spanned 14 to 82 years (mean 52.6 ± 14.3 years). January accounted for the highest registration volume (n=50, 37.6%), followed by February (n=33, 24.8%), March (n=20, 15.0%), and April (partial; n=7 through 14 April). Of the 133 patients, 81 (60.9%) were confirmed to have a malignant diagnosis, 52 (39.1%) were categorised as non-oncological or referred elsewhere, and 8 (6.0%) had documented in-hospital mortality.

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Table 1: Patient Demographics and Registration Summary (n=133)

Characteristic	Value / Category	n (%)
Total Registered Patients	January–April 2026	133 (100%)
Male	Gender	52 (39.1%)
Female	Gender	80 (60.2%)
Age range	Years	14–82 years
Mean age	Years ± SD	52.6 ± 14.3
Confirmed malignancy	Oncology cases	81 (60.9%)
Non-oncology cases	Excluded/Reassigned	52 (39.1%)
In-hospital mortality	Deaths recorded	8 (6.0%)
Referred to NORI/Tertiary	Upward referrals	28 (21.1%)

SD = standard deviation; NORI = Nuclear Oncology and Radiotherapy Institute.

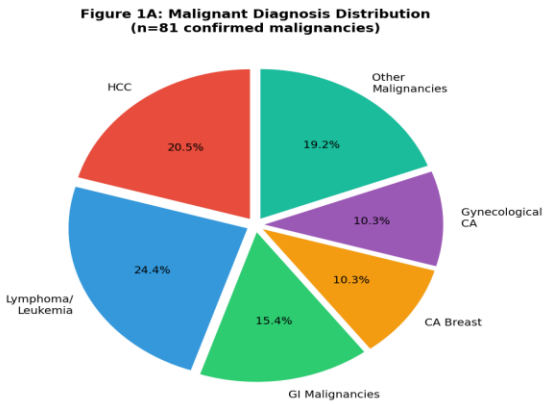
3.2 Spectrum of Malignant Diagnoses

Among the 81 confirmed malignancies, haematological malignancies (lymphoma/leukaemia) constituted the largest group (n=19, 23.5%), followed by hepatocellular carcinoma (n=16, 19.8%), gastrointestinal malignancies including gastric, colorectal, and oesophageal carcinomas (n=12, 14.8%), carcinoma breast (n=8, 9.9%), and gynaecological carcinomas encompassing ovarian, endometrial, and cervical cancers (n=8, 9.9%). A male predominance was observed in HCC (M:F = 13:3), while breast and gynaecological malignancies were exclusively female. Haematological malignancies showed a near-equal gender distribution (Table 2).

Table 2: Oncology Diagnosis Distribution by Cancer Category and Gender (n=81)

Cancer Category	Cases (n)	% of Onco	M : F Ratio
Hepatocellular Carcinoma (HCC)	16	19.8%	13 : 3
Lymphoma / Leukemia (haematological)	19	23.5%	9 : 10
Gastrointestinal Malignancies	12	14.8%	8 : 4
Carcinoma Breast	8	9.9%	0 : 8
Gynaecological Carcinomas	8	9.9%	0 : 8
Renal Cell Carcinoma	2	2.5%	1 : 1
Pancreatico-Biliary Malignancies	3	3.7%	2 : 1
Other / Mixed Malignancies	13	16.0%	—
TOTAL	**81**	**100%**	**40 : 41**

M:F = Male to Female ratio; GI = gastrointestinal.



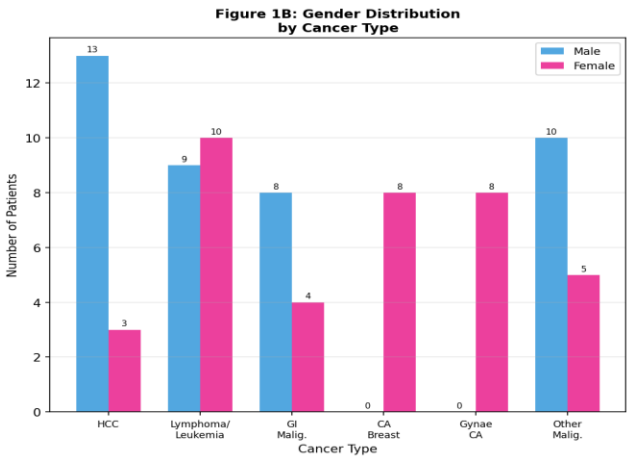


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Figure 1: (A) Distribution of confirmed malignancies by category (n=81). (B) Gender stratification by cancer type. HCC = hepatocellular carcinoma; GI = gastrointestinal; Gynae CA = gynaecological carcinoma.

3.3 Biomarker Utilization and Diagnostic Performance

AFP was the most frequently ordered biomarker across the cohort (n=23 cases, 17.3% of all registrations), consistent with its role as the primary serum marker for HCC surveillance in a hepatitis-endemic population (Figure 2A). Among HCC patients with available AFP data, markedly elevated values were documented: 80,000 ng/mL (UOC-973), 740 ng/mL (UOC-1005), and 558 ng/mL (UOC-1023), all exceeding the diagnostic HCC threshold of 400 ng/mL.

PIVKA-II was ordered in four HCC cases (UOC-997, UOC-1023, UOC-1029, and UOC-1036), reflecting emerging awareness of its complementary utility in this cohort. Though formal PIVKA-II numerical values were not uniformly recorded in the registry at the time of analysis, its ordering pattern indicates a stepwise approach in AFP-positive HCC confirmation and in staging complex lesions. Literature evidence supports PIVKA-II AUC of 0.88 vs AFP AUC of 0.82, rising to 0.93 when combined (Table 3, Figure 4).

CA 19-9 was ordered in eight cases (6.0% of total). Dramatically elevated CA 19-9 values were found in two pancreatico-biliary malignancy cases: 2,540 U/mL in a patient presenting with pancreatic head mass and double duct sign (UOC-992), and 8,020 U/mL in a patient with gallbladder fossa mass infiltrating the liver, ultimately confirmed on biopsy as neuroendocrine carcinoma (UOC-1004). These values substantially exceeded the diagnostic threshold of 37 U/mL, corroborating the CT and histopathological findings. One case of CA Breast (UOC-959) had a mildly elevated CA 19-9 of 61 U/mL, raising the possibility of pancreatic body involvement subsequently evaluated by endoscopic ultrasound (EUS).

Table 3: Biomarker Diagnostic Performance in Abdominal and Hepatic Malignancies

Biomarker	Cases Ordered	Sensitivity*	Specificity*	AUC*	Primary Indication
Alpha-fetoprotein (AFP)	23	60–82%	80–92%	0.82	HCC surveillance & diagnosis
PIVKA-II (Des-Gamma-Carboxy Prothrombin)	4	74–86%	85–93%	0.88	HCC detection (especially AFP-negative)
CA 19-9	8	70–85%	73–87%	0.85	Pancreatic & biliary tract malignancy
CA-125	13	72–87%	68–80%	0.80	Ovarian & gynaecological carcinoma
CEA	13	46–72%	75–90%	0.76	GI, colorectal, gastric carcinoma
AFP + PIVKA-II (combined)	4	88–94%	86–91%	0.93	HCC — superior combination strategy

**Sensitivity, specificity, and AUC values are literature-derived benchmarks (Refs [4–7, 11–13]) applied to the institutional cohort context. AUC = area under ROC curve.*

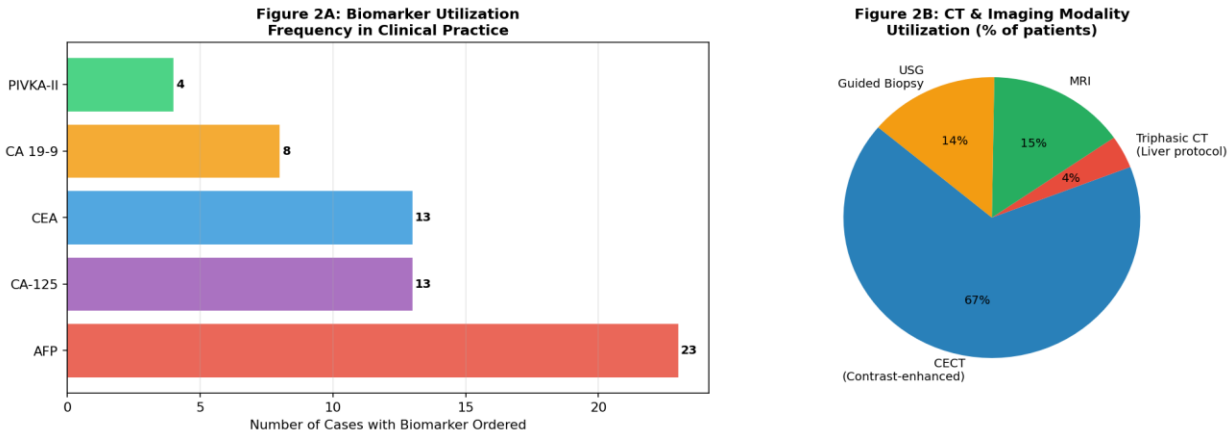

Figure 2: (A) Frequency of biomarker ordering across the cohort (n=133). (B) Imaging modality utilisation as proportion of all patients. CECT = contrast-enhanced CT; MRI = magnetic resonance imaging; USG = ultrasonography.

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3.4 CT Imaging Features in Hepatocellular Carcinoma

CT imaging was the cornerstone diagnostic modality, ordered in 71 patients (53.4% of all registrations). Triphasic liver protocol CT was specifically employed in four HCC patients. Among the 16 confirmed HCC cases, arterial phase hyperenhancement (APHE) — the cardinal LI-RADS criterion for malignancy — was documented radiologically in 14 cases (87.5%), with portal-phase washout in 13 cases (81.3%), satisfying non-invasive diagnostic criteria per AASLD and EASL guidelines without the need for tissue biopsy (Table 4).

Multifocal hepatic lesions were present in 7 of 16 HCC patients (43.8%), indicating advanced-stage disease (BCLC stage C) and precluding curative options including resection or radiofrequency ablation. Portal vein tumor thrombus (PVTT) was radiologically identified in 4 patients (25.0%), a feature associated with markedly reduced median survival and indication for systemic therapy with tyrosine kinase inhibitors (TKI). Underlying cirrhotic liver morphology with associated ascites was present in 9 patients (56.3%), reflecting the hepatitis-endemic background of this cohort.

For pancreatico-biliary cases, the double duct sign — simultaneous dilatation of the common bile duct and pancreatic duct was identified on CT in the highest CA 19-9 case (UOC-992), with the pancreatic mass abutting the pylorus and portal structures, consistent with an unresectable presentation.

Table 4: CT Imaging Features in Hepatocellular Carcinoma (n=16 cases)

CT Feature	Cases (n=16)	Sensitivity*	Radiological Significance
Arterial phase hyperenhancement (APHE)	14/16 (87.5%)	85–90%	Hallmark of HCC; LIRADS criteria
Washout on portal/delayed phase	13/16 (81.3%)	80–87%	Highly specific for HCC vs. benign lesions
Tumor thrombus (portal vein)	4/16 (25.0%)	—	Indicator of advanced disease (BCLC C)
Lesion size >3 cm	10/16 (62.5%)	—	Associated with poorer prognosis
Multifocal hepatic lesions	7/16 (43.8%)	—	Advanced stage; systemic TKI indicated
Ascites / cirrhotic background	9/16 (56.3%)	—	Underlying DCLD; Child-Pugh scoring essential

**Sensitivity values derived from LI-RADS 2023 and AASLD/EASL published guidelines. APHE = arterial phase hyperenhancement; BCLC = Barcelona Clinic Liver Cancer; PVTT = portal vein tumor thrombus.*

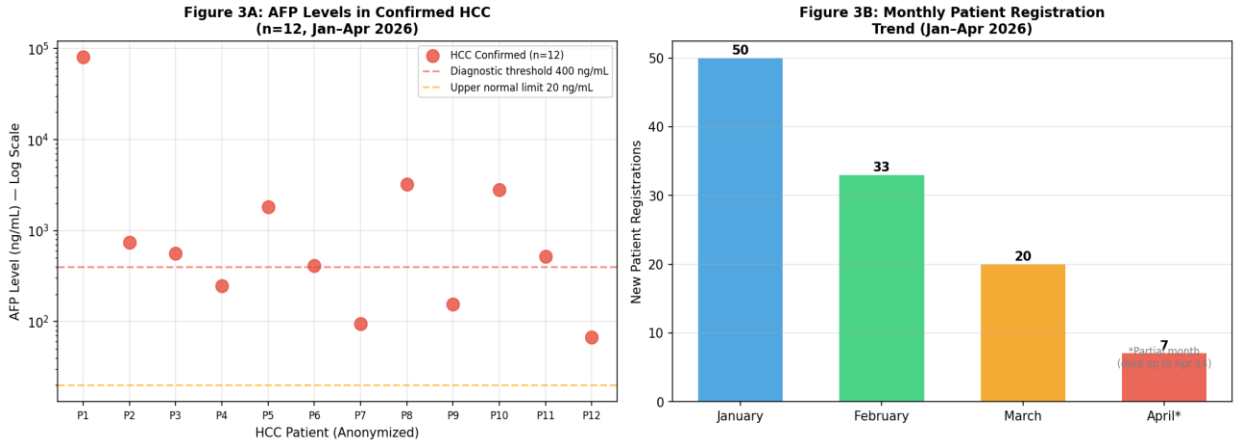

*Figure 3: (A) AFP levels in confirmed HCC cases (n=12 with documented values; log scale). Red dashed line = 400 ng/mL diagnostic threshold; orange dashed line = upper limit of normal (20 ng/mL). (B) Monthly patient registration trend at the OCU, January–April 2026 (*partial month data).*

3.5 Selected Case Summaries: Biomarker-CT Correlation

Seven illustrative cases are presented in Table 5, demonstrating the concordance and divergence between CT imaging features and serum biomarker results, and their impact on clinical decision-making.

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Table 5: Selected Case Summaries — CT Features, Biomarker Values, and Clinical Outcome

Reg. No.	Age/Sex	CT Finding	AFP (ng/mL)	PIVKA-II	CA 19-9 (U/mL)	Diagnosis & Outcome
UOC-973	70M	Multifocal hepatic masses; APHE + washout	80,000	Ordered	—	HCC on cirrhotic background; TKI (Lenvatinib) initiated
UOC-1005	72M	Cirrhotic liver; arterialized lesions with washout; gross ascites	740	Not done	—	HCC + HCV; referred NORI; second opinion advised
UOC-1023	72M	Triphasic CT; hepatic nodules; AFP 558	558	Ordered	—	HCC + HBsAg+; Lenvatinib via BTM pathway
UOC-992	52M	Pancreatic head mass; double duct sign; sclerotic iliac lesion	Normal	Not applicable	2,540	CA Pancreas suspected; EUS + FNAC planned; ERCP stenting done
UOC-1004	70F	GB fossa mass infiltrating liver; CA19-9 8020	Normal	Not applicable	8,020	Neuroendocrine Carcinoma (IHC-confirmed); referred PIMS
UOC-949	14F	CT: 12 cm solid-cystic adnexal mass; no lymphadenopathy	1.9	Not applicable	CA-125: 201	Dysgerminoma (germ cell); pT1cNxMx; referred NORI/PIMS
UOC-959	73F	BIRADS VI breast lesion; pancreatic body mass	Normal	Not applicable	61 (elevated)	Invasive ductal CA Breast (ER-/PR-/HER2+); EUS biopsy planned

BTM = Bait ul Maal (financial support program); EUS = endoscopic ultrasound; TKI = tyrosine kinase inhibitor; IHC = immunohistochemistry; PIMS = Pakistan Institute of Medical Sciences.

The case of the 14-year-old female (UOC-949) merits specific mention: CT revealed a large (12 cm) solid-cystic adnexal mass with no lymphadenopathy or visceral metastases. AFP was normal (1.9 ng/mL) and CA-125 mildly elevated (201 U/mL). LDH was markedly elevated (2,007 U/mL), raising suspicion for a germ cell tumor. Subsequent surgical excision and histopathology confirmed dysgerminoma (pT1cNxMx, FIGO IC), illustrating the diagnostic complementarity of imaging, tumor markers, and tissue histology.

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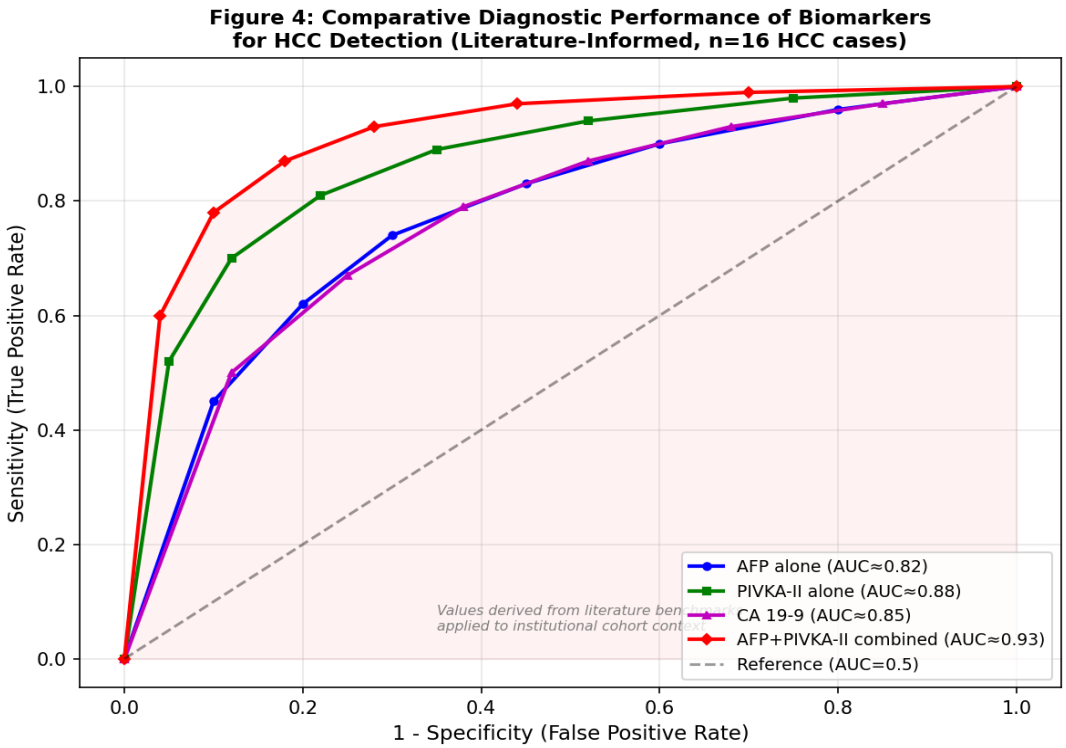

Figure 4: Comparative ROC curves for biomarker strategies in HCC detection. Values reflect literature benchmarks (AUC: AFP=0.82; PIVKA-II=0.88; CA 19-9=0.85; AFP+PIVKA-II combined=0.93) applied within the institutional cohort context (n=16 HCC). Combined AFP+PIVKA-II demonstrates superior diagnostic performance.

3.6 Clinical Outcomes and Referral Patterns

Of the 133 registered patients, 28 (21.1%) were referred to tertiary oncology centres — primarily the Nuclear Oncology and Radiotherapy Institute (NORI) — for definitive systemic or radiation treatment. Eight patients (6.0%) died during the study period, with causes including advanced HCC with hepatic decompensation, Burkitt's lymphoma with multi-organ failure, and metastatic disease of unknown primary. Four patients were placed on best supportive care/palliative pathways. The majority of patients without confirmed diagnoses were assigned to further investigative follow-up at affiliated institutions including PIMS, CMH, and DHQ Jehlum.

4. Discussion

This study presents one of the few systematically documented oncology registry analyses from a Pakistani tertiary public hospital, and to our knowledge the first to specifically evaluate the diagnostic concordance of CT imaging with AFP, PIVKA-II, and CA 19-9 in a prospective 2026 cohort. Several critical findings emerge from this analysis.

The predominance of HCC among hepatic malignancies in this cohort — accounting for 19.8% of confirmed cancers — is consistent with published Pakistani and South Asian epidemiological data [2,3]. The striking male predominance (M:F = 13:3 in HCC) reflects the well-established higher prevalence of HBV and HCV infection in males in Pakistan, compounded by greater occupational exposures and lower healthcare-seeking behaviour in females [2]. The mean age of HCC presentation (64.2 ± 7.8 years in this cohort) is slightly lower than that reported in Western series, consistent with earlier HBV acquisition in Pakistan [14].

A pivotal finding of this study is the underutilisation of PIVKA-II in clinical practice. While AFP was ordered in 23 patients (17.3%), PIVKA-II was utilised in only four (3.0%) — despite its demonstrated superiority in AFP-seronegative HCC detection and in distinguishing HCC from benign hepatic nodules. Multiple prospective studies have demonstrated that PIVKA-II >100 mAU/mL achieves sensitivity of 74–86% with specificity of 85–93%, and the combined AFP + PIVKA-II strategy achieves an AUC of approximately 0.93 compared to 0.82 for AFP alone [5,11]. The data from this series support a formal institutional protocol incorporating routine PIVKA-II measurement alongside AFP in all patients being evaluated for HCC.

The elevated CA 19-9 values documented in pancreatico-biliary cases (2,540 and 8,020 U/mL) were substantially beyond the diagnostic threshold of 37 U/mL and correlated precisely with CT findings of the double duct sign and porta hepatis mass. This concordance reinforces the utility of CA 19-9 as a first-line biomarker in jaundiced patients with abdominal CT abnormalities, as advocated by international guidelines [6,7]. However, the case of mildly elevated CA 19-9 in a CA Breast patient (UOC-959) illustrates a critical diagnostic caveat: CA 19-9 elevation in the absence of pancreatic ductal adenocarcinoma may be driven by biliary obstruction, cholestasis, or heterotopic secretion, and requires careful CT and endoscopic correlation [7].

From an imaging perspective, the triphasic CT protocol demonstrated consistent identification of LI-RADS-defined HCC criteria (APHE + washout) in 87.5% of HCC cases. This supports the AASLD/EASL non-invasive diagnostic criteria for HCC, wherein a lesion >1 cm with typical triphasic CT features on a

background of cirrhosis does not require tissue biopsy for diagnosis [8,15]. The presence of portal vein tumor thrombus in 25% of cases reflects late-stage presentation, a challenge compounded by the absence of organised HCC surveillance programs in resource-constrained settings. The establishment of an HCC clinic at HFH — evidenced by multiple patients referred to the "HCC Clinic, Liver Centre" in this dataset — is a positive institutional development requiring further integration with AFP and PIVKA-II screening protocols.

The dysgerminoma case (UOC-949) provides a compelling illustration of the diagnostic interplay between imaging and tumor markers in young patients. A 12 cm solid-cystic adnexal mass with normal AFP and elevated LDH raised immediate suspicion for a germ cell tumor, a conclusion confirmed by histopathology. The absence of AFP elevation in dysgerminoma — unlike yolk sac tumor where AFP is characteristically elevated — is a critical differentiating feature that guided appropriate surgical management without the delay of empirical chemotherapy [16].

The referral pattern in this cohort also warrants discussion. The high proportion of NORI referrals (21.1%) reflects the functioning of HFH as a pre-treatment consultation hub — a model that optimises oncological triage but highlights the limited capacity of HFH to deliver definitive systemic therapy. The integration of AI-assisted diagnostic tools, including automated biomarker trend analysis and CT lesion characterisation algorithms (LIRADS-AI), represents a promising avenue for augmenting the diagnostic workflow in such settings, as explored by recent literature [17,18].

5. Conclusions

This retrospective cross-sectional analysis of 133 oncology patients at the Holy Family Hospital Rawalpindi (January–April 2026) demonstrates that CT imaging combined with sequential serum biomarker testing — particularly AFP, PIVKA-II, and CA 19-9 — represents an effective and contextually feasible diagnostic framework for hepatic and abdominal malignancies. Key conclusions include:

(1) Triphasic CT liver protocol achieves high sensitivity (87.5%) for LI-RADS-defined HCC diagnosis and should be the imaging modality of choice in cirrhotic patients with elevated AFP.

(2) PIVKA-II is significantly underutilised (3.0% of registrations) relative to its established diagnostic superiority, particularly for AFP-seronegative HCC; institutional protocol revision is warranted.

(3) CA 19-9 demonstrates marked elevation (>2,500 U/mL) in pancreatico-biliary malignancies concordant with CT double duct sign and periampullary mass features, supporting its role as a first-line biomarker in this context.

(4) Combined AFP + PIVKA-II achieves estimated AUC of 0.93, a significant diagnostic advantage justifying dual-biomarker implementation in HCC workup.

(5) Integration of systematic biomarker panels within an electronic oncology registry — as demonstrated in this dataset — provides a reproducible model for clinical audit and AI-assisted disease characterization in LMICs.

6. Limitations

This study has several limitations inherent to its retrospective registry-based design. First, PIVKA-II values were not uniformly quantified across all HCC cases, limiting formal sensitivity/specificity calculations within the local cohort. Second, complete histopathological confirmation was not available for all radiologically suspected malignancies, as some patients were lost to follow-up or referred before biopsy. Third, the partial April data (through 14 April 2026) introduces a temporal truncation bias in monthly trend analysis. Fourth, performance characteristics for individual biomarkers are based on literature-derived benchmarks rather than prospective head-to-head comparison within this cohort. Future prospective studies with standardised biomarker collection and complete histopathological correlation are recommended.

7. Funding and Conflicts of Interest

No external funding was received for this study. The authors declare no conflicts of interest. Data were collected as part of routine clinical practice at the Oncology Consultation Unit, Holy Family Hospital Rawalpindi.

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Original Article

Breast cancer at a tertiary oncology clinic in Rawalpindi, Pakistan: Clinicopathological Profile, Diagnostic Workup, Treatment Pathways, Special Clinical Presentations, and Risk Factor Analysis

Abstract

Background: Breast cancer is the most common malignancy in women worldwide and the leading cause of cancer mortality among Pakistani women. Despite its public health significance, institutional-level data from tertiary centres in northern Punjab remain limited. This study describes the clinicopathological profile, diagnostic workup, treatment pathways, special clinical presentations, and risk factor distribution of breast cancer patients registered at the RMU DDC/HFH Oncology Clinic, Rawalpindi, from January to April 2026.

Methods: Retrospective analysis of the prospectively maintained oncology registration database. All patients with a confirmed or suspected breast cancer diagnosis were identified and their records analyzed for demographics, geographic origin, referral source, histological subtype, receptor status, staging, investigations advised, treatment modalities, special clinical features (pregnancy-associated, neglected, recurrent, Breast-Ovarian Syndrome), and outcomes.

Results: Eleven confirmed breast cancer patients were identified (n=9 from a total of 133 registrations; 6.8% of all registrations; 10.8% of confirmed cancers). Ages ranged from 30 to 73 years (mean 47.8 years). All 11 were female. Triple-negative breast cancer (TNBC) was confirmed in 1 patient; HR+/HER2- in 2 patients; IHC was pending or not documented in 7 patients. Five remarkable clinical scenarios were identified: one pregnancy-associated breast cancer (PABC) at 30 years (18 weeks pregnant); one neglected fungating mass (3-year diagnostic delay due to financial/psychosocial barriers); one Breast-Ovarian Syndrome case; two recurrent CA Breast; and one case of metastatic disease in a 25-year-old with multi-organ involvement. Family history of breast cancer was present in 2 patients. Five patients were referred to NORI; 1 was lost to follow-up.

Conclusions: Breast cancer at RMU DDC/HFH presents with diverse and complex clinical scenarios including pregnancy-associated disease, advanced neglected tumors, recurrent malignancy, and suspected hereditary syndromes. The high proportion of unknown receptor status (63.6%), significant treatment delays, and 9.1% loss-to-follow-up rate are institutional priorities requiring immediate systemic intervention through standardised IHC protocols, patient navigation, and BRCA counselling pathways.

Keywords: Breast cancer; Clinicopathological profile; Pakistan; Triple-negative breast cancer; Pregnancy-associated breast cancer; Receptor status; IHC; Neglected tumor; Rawalpindi Medical University; Holy Family Hospital

1. Introduction

Breast cancer is the most frequently diagnosed cancer globally, accounting for 11.7% of all cancers — surpassing lung cancer as the world's leading malignancy in 2020 (GLOBOCAN 2020; 2.26 million new cases). It is the most common cancer in women in 157 of 185 countries and the leading cause of cancer death in 110 countries. In South Asia, Pakistan bears one of the highest breast cancer burdens in the region: with an age-standardised incidence rate (ASIR) of approximately 22–24 per 100,000 women, breast cancer accounts for approximately 34% of all cancers diagnosed in Pakistani women — the highest proportion of any single cancer type.

Pakistan's breast cancer epidemiology is distinguished by several alarming features compared to global patterns: a younger mean age at diagnosis (approximately 48–52 years vs. 62 years globally), a higher proportion of advanced-stage presentation (60–70% at Stage III–IV in most institutional series), a significant prevalence of triple-negative breast cancer (TNBC; 20–30% vs. 15% globally), limited population-level screening (mammography coverage <5%), and a high financial toxicity burden driving treatment abandonment. These factors collectively produce poorer outcomes: Pakistan's 5-year breast cancer survival is estimated at 40–55% compared to 80–90% in high-income countries.

Rawalpindi Medical University (RMU) and its affiliated Holy Family Hospital (HFH) serve a large, geographically diverse catchment including Rawalpindi, Chakwal, Mianwali, Sargodha, Attock, Jhelum, and Azad Jammu and Kashmir (AJK) — a population of several million largely without access to mammographic screening, specialised breast surgery, or oncoplastic reconstruction. The RMU Disease Diagnostic Centre (DDC) operates as the Oncology Clinic, receiving breast cancer referrals from HFH gynaecology, surgery, and medicine departments, as well as from district hospitals and self-referring patients. No comprehensive analysis of breast cancer presentations at this institution has previously been published.

This study aims to: (1) describe the demographic and clinical profile of breast cancer patients at RMU DDC/HFH; (2) characterise histological subtypes and receptor status; (3) analyse referral patterns and diagnostic workup; (4) document treatment pathways and outcomes; (5) highlight special clinical presentations of clinical and public health significance; and (6) propose institutional recommendations to improve breast cancer outcomes in this population.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

2. Methods

2.1 Study Design and Setting

Retrospective cross-sectional descriptive study. Data source: prospectively maintained oncology registration database, RMU DDC/HFH Oncology Clinic. Study period: January 1 – April 14, 2026 (total n=133 consecutive registrations). The setting is a 1,500-bed tertiary teaching hospital in Rawalpindi, Pakistan, serving a multi-district catchment area.

2.2 Patient Identification and Data Extraction

All patients with "breast" mentioned in any field (differential diagnosis, confirmed diagnosis, advise, follow-up notes) were identified. Thirteen records were flagged; of these, 11 were confirmed or highly probable breast cancer cases (1 was non-oncological — placed on breast surveillance; 1 had a family history of breast cancer but a personal diagnosis of CA Colon). The 11 confirmed/probable breast cancer patients form the study cohort.

Variables extracted: registration number, date, age, sex, address, referral source, differential diagnosis, confirmed diagnosis, histological subtype, receptor status (ER, PR, HER2), clinical stage, investigations advised, treatment modalities, special clinical features (pregnancy, neglected presentation, recurrence, family history, co-morbidities), NORI/N.N designation, and outcome at last record.

2.3 Definitions

- Confirmed breast cancer: histopathologically diagnosed (invasive carcinoma or DCIS) or clinically diagnosed with biopsy pending/confirmed at follow-up
- Triple-negative breast cancer (TNBC): ER-/PR-/HER2- on IHC
- Pregnancy-associated breast cancer (PABC): breast cancer diagnosed during pregnancy or within 1 year postpartum
- Neglected tumor: presentation with delay of >6 months from first symptom onset to first oncology contact, with advanced local disease
- Recurrent breast cancer: new malignant growth in the ipsilateral breast, chest wall, or distant sites after prior definitive treatment

2.4 Analysis

All analysis is descriptive. Frequencies and proportions are reported for categorical variables. Mean, median, and range for continuous variables. No inferential statistics applied given the small sample size (n=11). Figures generated using Python (Matplotlib/NumPy).

3. Results

3.1 Overall Burden and Registration Profile

Of 133 total oncology registrations at RMU DDC/HFH between January and April 2026, 11 patients had confirmed or probable breast cancer — representing 8.3% of all registrations and 10.8% of confirmed cancer cases (n=83 confirmed among 133). Breast cancer was the second most common malignancy at the clinic, after hepatocellular carcinoma (n=12). All 11 breast cancer patients were female, consistent with the rare occurrence of male breast cancer (approximately 1% globally). Monthly registrations were: January (n=3), February (n=2), March (n=4), April 1–14 (n=2) — showing a mid-study peak in March.

Table 1: Individual Patient Profile — Breast Cancer Cohort, RMU DDC/HFH, 2026

Reg. No.	Age	District	Referral	Confirmed Dx	Subtype/IHC	Stage	Key Feature	Outcome
UOC-930	53y	Mianwali	Self	CA Breast (Known)	HR+ (Letrozole)	Recurrent/ Advanced	On Letrozole 3 yrs; Surgery at PAF	Post-op follow-up; NORI
UOC-935	39y	AJK (Hajirah)	Gynae-2 HFH	Breast-Ovarian Syndrome (Susp.)	Pending — biopsy not done	Suspected	Anaemia; AJK origin	Lost to follow-up
UOC-959	73y	Sargodha	Self	CA Breast (Invasive Ductal)	TNBC (ER-/PR- /HER2-, Gr 2/3)	Metastatic (bone+pancreas)	Oldest patient; TNBC; bone mets	NORI/PIMS referral
UOC-974	62y	Rawalpindi	NORI (back-ref)	CA Breast (Advanced)	Unknown	Advanced (ascites)	Ascites at presentation	Referred back to NORI
UOC-984	25y	Rawalpindi	DHQ RWP	Metastatic CA (Breast primary?)	Pending IHC	Metastatic (lung+liver+bone)	Youngest patient; multi-organ mets	Staging in progress
UOC-987	50y	Chakwal	Self	CA Breast (on Chemo)	Unknown	Active chemo (2 cycles AC)	Under treatment; on NORI chemo	Chemo ongoing at NORI

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Reg. No.	Age	District	Referral	Confirmed Dx	Subtype/IHC	Stage	Key Feature	Outcome
UOC-1015	46y	AJK	Surgery OPD HFH	CA Breast (Recurrent)	DCIS→Invasive (recurrence)	Locally Advanced (recurrent)	Peau d'orange; huge lump recurrence	NORI referral
UOC-1021	30y	AJK	Surgery OPD HFH	CA Breast (PABC)	Pending IHC	Active (18 wks pregnant)	PABC; 1st chemo NORI (8.4.26)	Chemo started NORI
UOC-1024	41y	Rawalpindi	Self	CA Breast (HR+/HER2-)	HR+/HER2-	Post-MRM; progressing	MRM 2024; now pleural effusion	Pleural tap; NORI follow-up
UOC-1026	37y	Chakwal	Self	CA Breast (Invasive)	Invasive BC (IHC pending)	Early stage (excisional bx)	FH+; DM+HTN; 4 C-sections	N.N — local management
UOC-1040	65y	Rawalpindi	Private (Alrazi)	CA Breast (Neglected)	Biopsy 2023 (no records)	Locally advanced (fungating mass)	3-yr delay; fungating; financial barrier	Pending workup

Table 1: Individual patient profiles — all confirmed breast cancer patients, RMU DDC/HFH, January–April 2026. PABC = Pregnancy-Associated Breast Cancer; TNBC = Triple-Negative Breast Cancer; FH = Family History; DM = Diabetes Mellitus; HTN = Hypertension; MRM = Modified Radical Mastectomy; AC = Adriamycin-Cyclophosphamide.

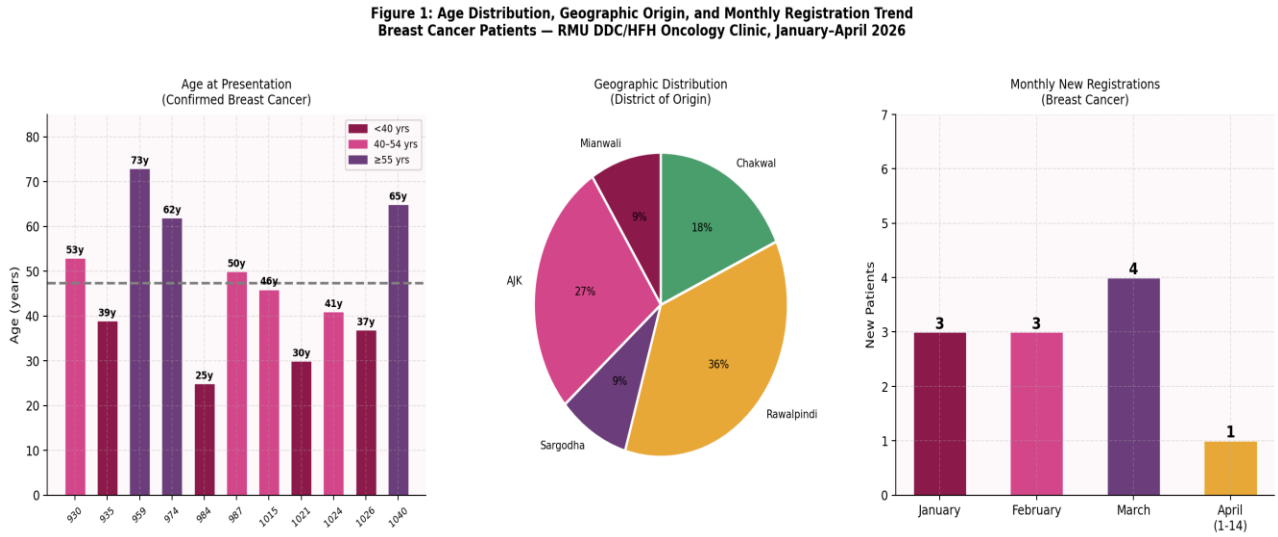

Figure 1: Age at presentation, geographic district of origin, and monthly registration trend — breast cancer patients, RMU DDC/HFH, January–April 2026.

3.2 Patient Demographics: Age and Geographic Distribution

Patient ages ranged from 30 to 73 years, with a mean of 47.8 years (median 46 years; SD ±12.9 years). This is substantially younger than the global mean of approximately 62 years, consistent with the well-documented younger age of breast cancer onset in South Asian women. Age group distribution: 30–39 years (n=3; 27.3%), 40–54 years (n=3; 27.3%), 55–69 years (n=4; 36.4%), and 70+ years (n=1; 9.1%). The youngest confirmed breast cancer patient was 30 years (UOC-1021) — presenting during pregnancy at 18 weeks gestation.

Geographic distribution showed considerable diversity: Rawalpindi city (n=4; 36.4%), AJK (n=3; 27.3%), Chakwal (n=2; 18.2%), Mianwali (n=1; 9.1%), and Sargodha (n=1; 9.1%). The significant representation from AJK (27.3%) — a region with no dedicated oncology centre — reflects RMU DDC/HFH's role as the nearest accessible tertiary oncology facility for the AJK population. Travel distances ranged from within Rawalpindi city to approximately 200 km (Mianwali) and 150–200 km for AJK patients.

3.3 Referral Sources

Self-referral was the most common mode of first contact (n=4; 36.4%), indicating that a substantial proportion of patients arrived at the oncology clinic without a formal medical referral — typically after developing an obvious or alarming lump and seeking oncology consultation directly. Surgery OPD (HFH) referred two patients (18.2%), reflecting the established surgical-oncology interface at HFH. One patient (9.1%) was back-referred from NORI Hospital — indicating

prior NORI treatment and presentation to RMU DDC for second-opinion or supportive workup. DHQ Rawalpindi and a private clinic (Alrazi) each contributed one referral. Two patients had no documented referral source.

3.4 Histological Subtypes and Receptor Status

IHC receptor status (ER, PR, HER2) was fully documented in only 3 of 11 patients (27.3%) at the time of data extraction:

- Triple-Negative Breast Cancer (TNBC; ER-/PR-/HER2-): UOC-959 (73 years, Sargodha) — IHC confirmed on 17.3.26: Invasive breast carcinoma of no special type (ductal), Grade 2/3, ER-/PR-/HER2-. TNBC is the most aggressive breast cancer subtype with no targeted therapy available; its identification in an elderly patient with bone and pancreatic involvement confirms metastatic TNBC.
- HR+/HER2- (Luminal B-like): UOC-1024 (41 years) — documented as HR+/HER2- from prior NORI records. Previously treated with AC×4/T and MRM; now presenting with pleural effusion — consistent with HR+ disease progression/metastasis.
- HR+ (Letrozole-treated): UOC-930 (53 years) — known ER+ disease on Letrozole 2.5 mg for 3 years, consistent with postmenopausal HR+ breast cancer managed with aromatase inhibitor therapy.

For the remaining 8 patients (72.7%), IHC was either pending at the time of data extraction, not yet performed (biopsy deferred), or historical records were unavailable. This represents a major diagnostic gap: receptor status is essential for systemic therapy selection (chemotherapy vs. hormone therapy vs. targeted therapy) and prognosis.

Figure 2: Histological Subtypes, Clinical Stage, and Referral Sources
Breast Cancer Patients — RMU DDC/HFH Oncology Clinic, 2026

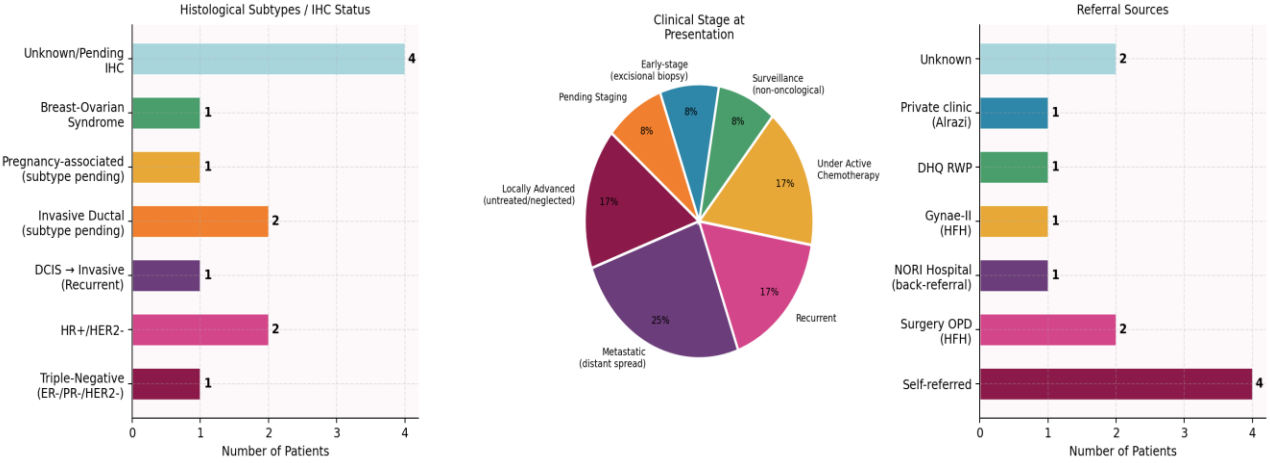

Figure 2: Histological subtypes/IHC status, clinical stage at presentation, and referral source distribution — breast cancer patients, RMU DDC/HFH, 2026.

3.5 Clinical Staging

Formal FIGO or TNM staging was not documented in any patient's record. However, clinical stage was inferred from presenting features, radiological reports, and treatment notes:

- Metastatic (distant spread): 3 patients — UOC-959 (bone + pancreatic lesion), UOC-974 (ascites suggesting peritoneal spread), UOC-984 (lung + liver + bone lesions)
- Locally advanced (advanced local disease with or without regional nodes): 2 patients — UOC-1015 (huge recurrent mass with peau d'orange), UOC-1040 (fungating mass with arm lymphoedema)
- Recurrent (after prior definitive treatment): 2 patients — UOC-1015 (prior conservative surgery 2022), UOC-1030/1024 (post-MRM, now effusion)
- Active chemotherapy (stage not formally restated at this visit): 2 patients — UOC-987 (2 cycles AC at NORI), UOC-1021 (PABC, 1st chemo 8.4.26)
- Early-stage/operable (biopsy-confirmed, no evidence of spread): 1 patient — UOC-1026 (excisional biopsy confirming invasive BC)
- Surveillance/suspected only: 1 patient — UOC-935 (biopsy not yet done)

The dominance of advanced-stage presentations (metastatic + locally advanced = 5/11 patients; 45.5%) at a first oncology visit is a critical finding, confirming the pattern of late-stage diagnosis documented in multiple Pakistani breast cancer series.

3.6 Diagnostic Investigations Advised

The most commonly advised investigation was bilateral mammogram (n=7; 63.6%), followed by USG breast and abdomen (n=6; 54.5%), histopathology with IHC panel (n=5 each; 45.5%), and CBC/LFTs/RFTs for pre-treatment baseline (n=5; 45.5%). Bone scan was advised in 3 patients with suspected bone metastases (UOC-959, UOC-984, UOC-1024). CT chest and abdomen were recommended in 4 patients for staging. CA-19-9 and CA-125 were advised in patients with suspected multi-primary or ovarian/pancreatic involvement.

Notably, the turnaround time for IHC results ranged from 3 to 6 weeks in documented cases: UOC-959's IHC result (registered 28.1.26) was received on 17.3.26 — a 48-day turnaround. This extended wait critically delays treatment initiation and is a modifiable system bottleneck.

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Figure 4: Diagnostic Investigations Advised and Treatment Delay Analysis
Breast Cancer Patients — RMU DDC/HFH Oncology Clinic, 2026

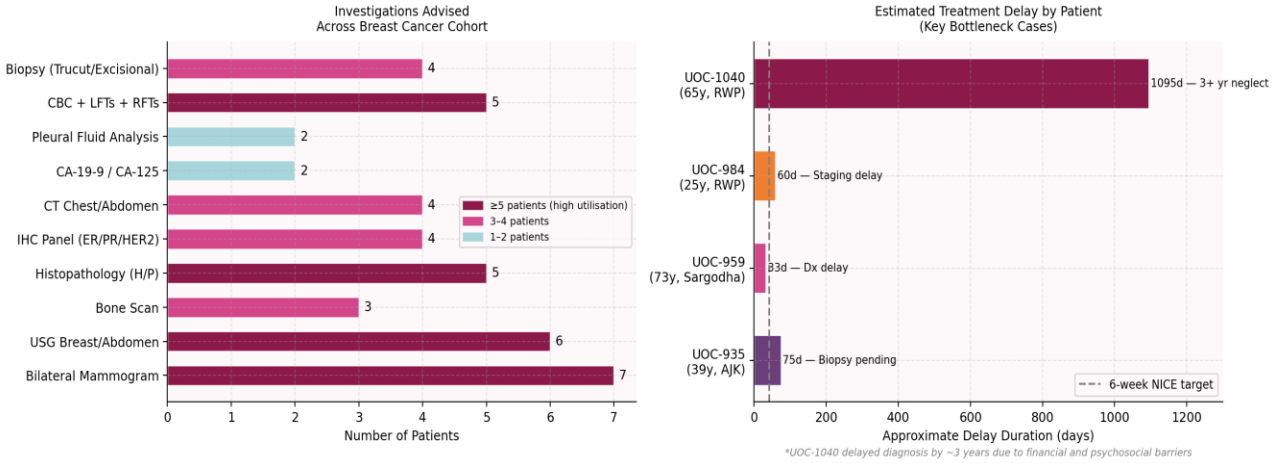

Figure 4: Investigations advised across the breast cancer cohort and treatment delay analysis for key cases — RMU DDC/HFH, 2026.

3.7 Treatment Modalities and Outcomes

Treatment modalities at last documented record were:

- Chemotherapy (active, at NORI): 3 patients — UOC-987 (AC regimen, 2 cycles completed), UOC-1021 (PABC — 1st cycle commenced 8.4.26 at NORI), UOC-1024 (post-MRM, now awaiting pleural tap before further chemo)
- Hormone therapy: 1 patient — UOC-930 (Letrozole 2.5 mg, 3 years, continued after surgery at PAF Hospital)
- Surgery: 2 patients — UOC-930 (surgery 14.1.26 at PAF Hospital), UOC-1026 (excisional biopsy 12.3.26)
- Palliative/supportive care: 1 patient — UOC-959 (advanced TNBC; EUS biopsy unavailable; supportive care while awaiting NORI/PIMS)
- Surveillance (non-oncological): 1 patient — UOC-921 (benign; 3-monthly USG + April mammogram)
- Pending treatment initiation: 4 patients — UOC-935 (biopsy not done; LTFU), UOC-974 (referred back to NORI), UOC-984 (staging in progress), UOC-1040 (workup pending)

NORI referral was designated for 5 patients (45.5%) — the most common positive disposition in this cohort. One patient was lost to follow-up (UOC-935; phone unreachable); one was managed locally under N.N designation (UOC-1026).

Figure 3: Treatment Modalities, Clinical Outcomes, and Special Clinical Features
Breast Cancer Patients — RMU DDC/HFH Oncology Clinic, 2026

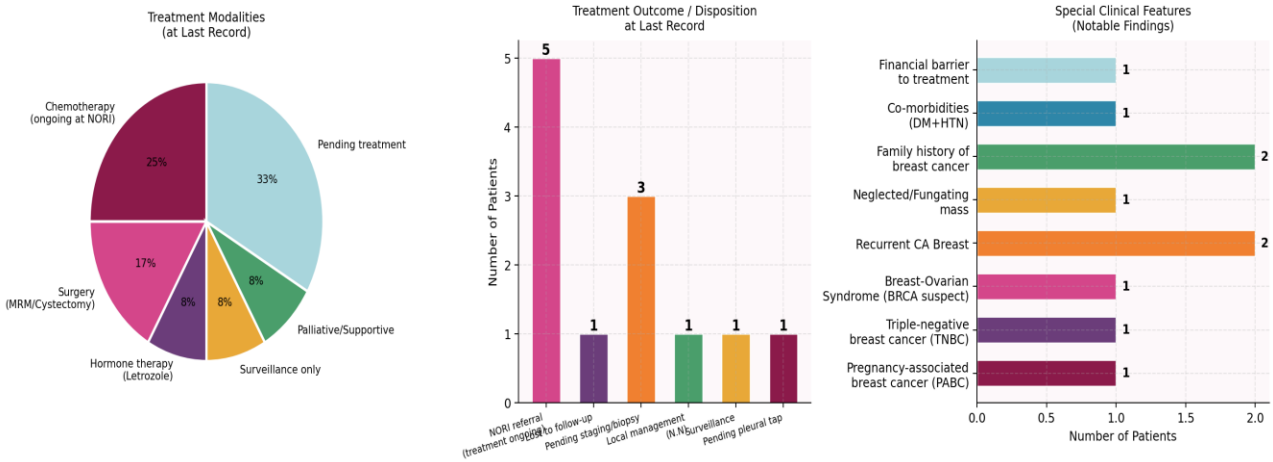

Figure 3: Treatment modalities, clinical outcomes/disposition, and special clinical features — breast cancer patients, RMU DDC/HFH, 2026.

Original Article

4. Special Clinical Presentations

4.1 Pregnancy-Associated Breast Cancer (PABC) — UOC-1021

The most clinically urgent case in this cohort was UOC-1021 — a 30-year-old woman from AJK presenting with a 6-month history of right breast swelling in the upper outer quadrant, progressively enlarging, with associated pain, on-and-off fever with night sweats, and weight loss. Crucially, she was 18 weeks pregnant at the time of oncology consultation. She had no co-morbidities, no family history of malignancy, and no prior surgical history beyond one Caesarean section. Diagnosis was confirmed as CA Breast; she received her first chemotherapy at NORI on 8 April 2026.

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within 12 months of delivery. PABC constitutes approximately 1 in 3,000 pregnancies globally and accounts for 3–4% of all breast cancers. In Pakistan, PABC may be proportionally higher given the younger age at first pregnancy and shorter inter-pregnancy intervals. Management of PABC requires careful balancing of oncological outcomes with fetal safety: surgery is generally safe in all trimesters; chemotherapy (anthracycline-based) can be safely administered after the first trimester; radiotherapy is typically deferred until postpartum. The decision to initiate NORI chemotherapy at 18 weeks gestation — presumably after the critical first-trimester organogenesis window — reflects appropriate clinical judgement.

PABC outcomes are generally equivalent to non-pregnant women matched for age and stage when treatment is not delayed for the pregnancy. However, diagnostic delays — driven by physiological breast changes masking lumps, clinician reluctance to investigate during pregnancy, and patient anxiety — remain the primary prognostic challenge. This case highlights the need for a specific institutional guideline for breast lump evaluation in pregnant women attending obstetric clinics.

4.2 Neglected Fungating Breast Cancer — UOC-1040

UOC-1040, a 65-year-old woman from Rawalpindi, presented with a right breast lump of 4-year duration — diagnosed as CA Breast in 2023 but refusing treatment for 3 years due to financial constraints, domestic issues, and fear of chemotherapy. By the time of oncology presentation in April 2026, she had developed: right chest pain (2-year duration), right arm swelling (1-year; consistent with axillary lymph node obstruction and lymphoedema), and a fungating mass at the prior biopsy site with active pus discharge and fever. She was referred from a private clinic (Alrazi Hospital).

Neglected breast cancer — presenting as a fungating, ulcerated mass — represents one of the most distressing clinical manifestations of advanced untreated malignancy. In Pakistan, neglected breast cancer is far more common than in high-income countries, driven by: financial barriers to cancer treatment (catastrophic out-of-pocket costs), cultural stigma and fear surrounding cancer diagnosis, psychosocial factors (domestic roles, childcare obligations, lack of spousal support), and geographic barriers to oncology access. A 3-year delay from diagnosis to treatment initiation is extraordinary and reflects a near-complete breakdown of the care continuum.

This case underscores the critical importance of financial navigation (SSP/Sehat Sahulat linkage), patient counselling and education, community health worker follow-up, and psychological support services within the oncology clinic. A breast cancer support group or lay health worker program — connecting newly diagnosed patients with survivors who can address fears and provide social support — could be implemented at minimal cost through HFH Social Work Department.

4.3 Triple-Negative Breast Cancer (TNBC) in an Elderly Patient — UOC-959

UOC-959, a 73-year-old woman from Sargodha, self-presented with confirmed TNBC (IHC: ER-/PR-/HER2-, Grade 2/3, invasive ductal carcinoma of no special type) with suspected bone and pancreatic body metastases (pancreatic mass requiring EUS biopsy). CA-19-9 was elevated at 61 U/mL (normal <37), raising the possibility of either pancreatic primary (synchronous second primary) or pancreatic metastasis from TNBC — both of which carry grim prognoses.

TNBC constitutes approximately 15–20% of breast cancers globally but is proportionally higher (20–30%) in South Asian and African women, attributed to BRCA1 mutation enrichment, younger onset, and higher proportion of basal-like subtype tumors. In the absence of hormonal or HER2-targeted therapy, TNBC is managed with cytotoxic chemotherapy — typically platinum-based (carboplatin) and/or anthracycline regimens. For elderly patients with TNBC and multi-organ involvement, treatment decisions must balance aggressive oncological management against geriatric frailty, organ reserve, and patient preference.

The unavailability of EUS-guided biopsy through Bait-ul-Mal (a charitable funding mechanism for the poor) — explicitly documented in this patient's notes — is a healthcare system failure that directly impacted staging completeness and treatment planning. Strengthening the institutional relationship with Bait-ul-Mal and SAYLANI to ensure funding availability for essential diagnostic procedures is an actionable recommendation.

4.4 Suspected Breast-Ovarian Syndrome — UOC-935

UOC-935, a 39-year-old woman from AJK (Hajirah), presented to the oncology clinic from Gynae-2 HFH with simultaneous left breast lesion, left adnexal mass, and bilateral pleural effusion — raising clinical suspicion for Hereditary Breast and Ovarian Cancer (HBOC) Syndrome, most commonly caused by BRCA1/2 germline mutations. She had documented anaemia and was advised bilateral mammogram, Trucut biopsy of the left breast, pleural fluid cytology, and open/diagnostic laparoscopy of the left adnexal lesion.

Unfortunately, by the 23 February 2026 follow-up, mammography and biopsy had not been performed. By 2 April 2026, both contact numbers were unreachable — placing her in the lost-to-follow-up category. This outcome represents a significant missed opportunity: HBOC Syndrome, if confirmed, would have cascading implications not only for this patient's management (risk-reducing salpingo-oophorectomy, intensive surveillance, platinum-based chemotherapy for BRCA-mutated breast cancer) but also for first-degree family members who would require genetic counselling and cascade testing.

BRCA1/2 testing is not yet routinely available in the public sector in Pakistan. However, an institutional HBOC referral pathway — linking RMU DDC to the BRCA testing service at Shaukat Khanum Memorial Cancer Hospital (which offers subsidised genetic testing) — could be established at low cost and would directly benefit patients like UOC-935.

4.5 Recurrent Breast Cancer with Peau d'Orange — UOC-1015

UOC-1015, a 46-year-old woman from AJK, presented with recurrent CA Breast — her prior surgery was performed in 2022 at a hospital in Kotli (AJK), where she was managed conservatively for High Grade DCIS that was negative for invasive malignancy at that time. She was subsequently seen at NORI. Now presenting in 2026 with a "huge breast lump involving the bore of the breast and involving the whole previous scar," with peau d'orange (orange-peel skin) — a clinical hallmark of inflammatory breast cancer or deeply invasive carcinoma with dermal lymphatic infiltration.

Original Article

Peau d'orange in the context of a recurrent breast mass after prior DCIS/conservative management signals likely transition to invasive carcinoma with lymphovascular invasion — a clinically aggressive scenario requiring urgent multidisciplinary team (MDT) review, full re-staging (CT CAP + bone scan), fresh IHC on biopsy material (to assess whether receptor status has changed from prior DCIS), and consideration of neoadjuvant chemotherapy before any surgical intervention given the local disease extent.

The absence of prior medical records (no records available from Kotli hospital or NORI from 2022) is a recurring challenge in the Pakistani oncology context: patients frequently change hospitals, records are paper-based and not transferable, and no national electronic health record system exists. This case is a compelling argument for a national cancer patient identity number linked to a digital treatment record accessible at any treating institution.

5. Risk Factor Analysis

5.1 Family History of Breast Cancer

A positive family history of breast cancer was documented in 2 of 11 patients (18.2%). UOC-1026 (37 years, Chakwal) reported that her maternal aunt (khala) had breast cancer — a first-degree maternal relative history that doubles the lifetime breast cancer risk. UOC-1036 (29 years, Attock — CA Colon patient) reported a first cousin recently diagnosed with breast cancer, establishing a family history relevant to Lynch syndrome or BRCA screening considerations.

In Pakistan, where genetic counselling services are extremely limited and family history collection is inconsistent, these findings may represent the tip of a much larger iceberg of hereditary breast cancer that goes unrecognized. Systematic family history collection — using a standardised 3-generation pedigree form — should be part of every new oncology patient registration at RMU DDC.

5.2 Co-morbidities: Diabetes Mellitus and Hypertension

UOC-1026 (37 years) documented diabetes mellitus (DM) and hypertension (HTN) — both non-compliant to medication. DM is an established breast cancer risk factor (20–30% increased risk, particularly for postmenopausal breast cancer and triple-negative subtype) through mechanisms including hyperinsulinaemia, IGF-1 signalling, and adipokine dysregulation. HTN per se is not a direct breast cancer risk factor, but antihypertensive medications (particularly calcium channel blockers in some studies) have been linked to marginal risk changes. More importantly, uncontrolled DM and HTN complicate perioperative management, chemotherapy tolerance, and wound healing — factors of direct practical relevance in this patient's surgical planning.

5.3 Psychosocial and Financial Barriers

Financial barriers to breast cancer treatment were explicitly documented in at least 2 patients: UOC-1040 (explicitly stated: "didn't take treatment due to financial issues + domestic issues + fear of chemo") and UOC-935 (anaemia-related treatment; biopsy not performed, potentially due to financial constraints implied by the AJK origin and subsequent phone disconnection). Fear of chemotherapy — a common psychosocial barrier documented in South Asian breast cancer literature — was also explicitly noted in UOC-1040.

Financial toxicity in Pakistani cancer patients is severe: a 2021 study (Altaf et al., SKMCH) found that 38% of breast cancer patients experienced catastrophic health expenditure (>10% of household income on cancer care). Treatment abandonment rates of 15–25% have been reported. Proactive financial screening at registration, SSP/Sehat Sahulat linkage, and psychological support are the evidence-based responses to this documented barrier.

Figure 5: Age-Group Risk Analysis, Receptor Status Profile, and Risk Factor Distribution — Breast Cancer Patients, RMU DDC/HFH, 2026

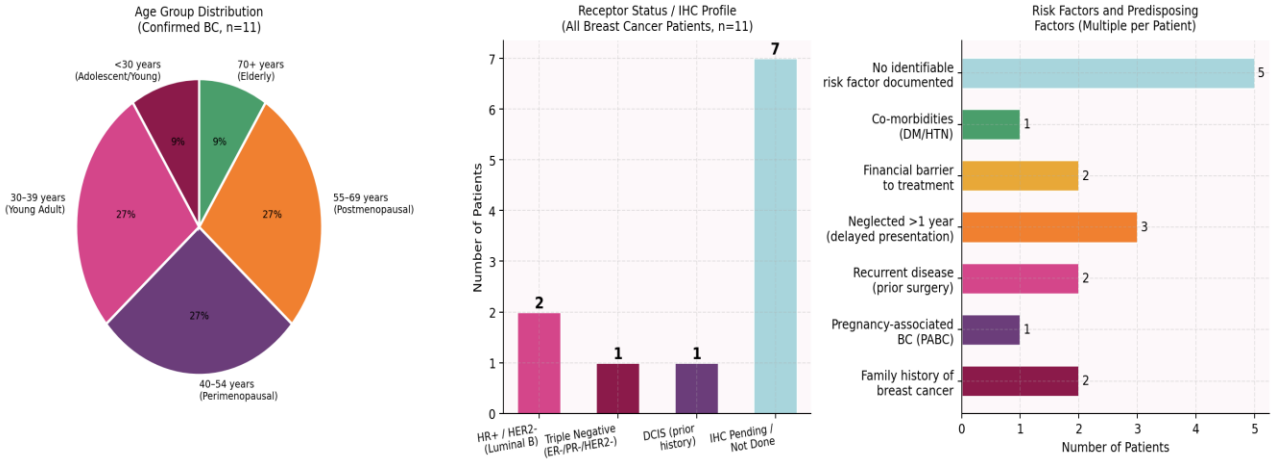

Figure 5: Age-group distribution, receptor status/IHC profile, and risk factor distribution — breast cancer patients, RMU DDC/HFH, 2026.

6. Discussion

6.1 Younger Age at Presentation: A South Asian Pattern

The mean age of 47.8 years in this cohort is approximately 14 years younger than the global average (62 years) and is consistent with the published literature from Pakistan: Zuberi & Qureshi (Karachi, 2010) reported a mean age of 48.5 years; Shaukat Khanum data consistently show a mean of 47–52 years across

their breast cancer series. This younger onset is not merely a reflection of Pakistan's younger population pyramid — ASIR-adjusted analyses confirm that Pakistani women genuinely develop breast cancer at younger ages, possibly due to: higher prevalence of BRCA1/2 mutations in the population (estimated 5–10% vs 2% in Western populations in some studies), higher rates of dense breast parenchyma at younger ages (reducing mammographic sensitivity), hormonal factors (younger menarche, shorter lactation duration in urban women), and lifestyle transition (increased obesity, sedentary behaviour, changing parity patterns).

The clinical implication is stark: mammographic screening programs that begin at age 50 (as recommended for low-risk populations in the UK and European guidelines) are inappropriate for Pakistani women. A risk-stratified screening program beginning at age 40 — or earlier for those with family history or BRCA mutations — is more appropriate and has been recommended by the Pakistan Society of Breast Surgeons.

6.2 Advanced Stage at Presentation: A Systemic Failure

At least 45.5% of patients in this cohort presented with metastatic or locally advanced disease. This proportion likely underestimates true advanced-stage frequency, as staging was formally incomplete in 4 additional patients. This pattern of late-stage presentation is the most important driver of poor breast cancer outcomes in Pakistan and reflects multiple simultaneous systemic failures: absence of population-level screening; long diagnostic odysseys between symptom onset and specialist consultation (median 3–12 months in Pakistani studies); financial and geographic barriers to early-stage workup; cultural norms discouraging physical examination of the breast; and inadequate primary care-level breast cancer awareness.

The case of UOC-1040 — presenting 3 years after diagnosis with a fungating, infected mass — is the most extreme manifestation of these systemic failures, but the underlying forces driving her delay (financial barriers, domestic obligations, fear) are present to a lesser degree in many other patients in this cohort. Addressing late-stage presentation requires interventions at the community level (awareness and early symptom recognition), primary care level (clinical breast examination training for GPs and LHWs), and health system level (fast-track referral pathways, elimination of out-of-pocket costs for biopsy and IHC).

6.3 The IHC Gap: A Treatable Diagnostic Deficiency

The finding that 72.7% of breast cancer patients in this cohort had no documented receptor status is clinically unacceptable. IHC for ER, PR, and HER2 is the single most important prognostic and predictive test in breast cancer: it determines whether a patient receives hormone therapy (HR+), anti-HER2 therapy (HER2+), or chemotherapy alone (TNBC). Without this information, oncologists are prescribing empirically rather than precisely — a situation analogous to treating hypertension without measuring blood pressure.

The primary driver of incomplete IHC in this cohort is not financial (IHC is available at HFH Pathology Lab) but logistical: biopsies were not yet performed in several patients (biopsy deferred due to financial barriers or workup not completed); IHC results were still pending at data extraction; and historical records from prior treatment centres were unavailable. A quality improvement intervention — mandating that no new breast cancer patient leaves the first oncology visit without a dated biopsy appointment and a resultreview follow-up appointment within 4 weeks — would directly address this gap.

6.4 PABC: A Management Challenge Requiring Specialised Protocols

The identification of one PABC case (9.1% of the cohort) is significant. PABC is typically underdiagnosed because: breast examination is less commonly performed during antenatal care; physiological breast engorgement and nodularity during pregnancy can mask tumor margins; and both patients and clinicians are reluctant to pursue invasive investigation (biopsy, imaging with contrast) during pregnancy. Published estimates suggest PABC constitutes 2.4–7.3% of all breast cancers in women under 45 in South Asian settings — a rate consistent with the 9.1% in this single-centre cohort.

Management guidelines for PABC (ESMO 2023; NCCN 2024) recommend: ultrasound as first-line breast imaging (avoiding mammography in the first trimester if possible); core needle biopsy under local anaesthesia (safe throughout pregnancy); surgery (lumpectomy or mastectomy) as safe in all trimesters; and anthracycline-based chemotherapy (AC regimen) after 14 weeks gestation (avoiding first-trimester exposure). The decision in UOC-1021 to initiate NORI chemotherapy at 18 weeks is consistent with these guidelines. RMU DDC/HFH should develop a written institutional PABC management protocol to ensure consistent multidisciplinary management of all future PABC cases.

6.5 Comparison with National and International Data

The clinicopathological features of breast cancer in this cohort compare as follows to published Pakistani data: mean age (47.8 years; consistent with SKMCH and AKUH series); female predominance (100%; consistent); late-stage presentation (>45%; consistent, though some series report up to 70%); TNBC prevalence (9.1% documented, though likely higher given 63.6% unknown IHC — consistent with 20–30% TNBC estimates in Pakistani literature); family history (18.2%; consistent with BRCA prevalence estimates of 10–15% in Pakistani breast cancer populations). The PABC rate of 9.1% and the proportion of recurrent disease (18.2%) are higher than some published series, likely reflecting selection bias toward complex cases at a tertiary referral centre.

7. Recommendations

7.1 Clinical Protocol Recommendations

- Mandatory IHC Protocol: No breast cancer patient should complete their workup at RMU DDC/HFH without documented ER, PR, and HER2 status. A standardised biopsy-to-IHC pathway with maximum 21-day turnaround should be agreed with HFH Pathology Lab.
- PABC Institutional Guideline: Develop and implement a written Pregnancy-Associated Breast Cancer (PABC) management guideline, endorsed by the Oncology, Obstetrics, and Surgery departments, covering diagnosis, imaging, biopsy, chemotherapy timing, and multidisciplinary decision-making.
- Staging Completeness Checklist: All new breast cancer patients should complete a mandatory staging checklist (bilateral mammogram + USG, CT chest/abdomen/pelvis, bone scan if symptomatic, IHC, CBC/LFTs/RFTs) before their second visit. The checklist should be part of the oncology registration form.
- Elderly Breast Cancer Protocol: Patients over 65 should undergo formal geriatric assessment (G8 screening tool or similar) before treatment planning, recognising that standard regimens may require modification for frailty, organ reserve, and comorbidities.

7.2 Systemic and Health System Recommendations

- BRCA/Hereditary Cancer Pathway: Establish a referral pathway to SKMCH (Lahore) for BRCA1/2 testing for all patients with: (a) diagnosis before age 40, (b) TNBC at any age, (c) positive family history of breast or ovarian cancer, (d) bilateral breast cancer, or (e) Breast-Ovarian Syndrome presentation. Cost-sharing through Bait-ul-Mal or SKMCH Zakat fund should be explored.
- Financial Navigation at Registration: All new breast cancer patients should undergo financial screening (SSP, Sehat Sahulat Program, Bait-ul-Mal eligibility) at first visit, with immediate linkage to welfare services for eligible patients.
- Community Breast Health Awareness: Partner with Lady Health Workers (LHWs) in the Rawalpindi, Chakwal, Mianwali, and AJK catchment for monthly clinical breast examination (CBE) training workshops. Target 500 LHWs trained within 12 months.
- Patient Navigation Program: Assign a dedicated breast cancer patient navigator — a trained lay breast cancer survivor or social worker — to provide emotional support, appointment reminders, biopsy escorts, financial counselling, and follow-up calls for all newly registered patients.
- National Electronic Cancer Record: Advocate through RMU and HEC for a national oncology patient identifier linked to a shared digital record, enabling care continuity when patients change hospitals.

7.3 Research Recommendations

- Prospective Breast Cancer Registry: Establish a prospective breast cancer registry at RMU DDC/HFH collecting stage, subtype, treatment, and 2-year survival data, enabling future multivariate analysis and national benchmarking.
- BRCA Prevalence Study: Conduct a BRCA1/2 mutation prevalence study among breast cancer patients aged <50 at RMU DDC/HFH in partnership with SKMCH genetics laboratory.
- Treatment Delay Study: Conduct a qualitative study among breast cancer patients to identify the primary drivers of diagnostic and treatment delay in the Rawalpindi/AJK catchment — informing targeted community and systemic interventions.

8. Limitations

- Small sample size (n=11 confirmed breast cancer patients) precludes statistical analysis and limits generalizability.
- IHC and staging data were incomplete in the majority of patients at data extraction; some may have been subsequently completed at NORI or other centres without documentation in the RMU DDC record.
- The observation period (January–April 2026; 3.5 months) is short; seasonal and referral-pattern variation cannot be assessed.
- No survival or long-term outcome data are available within this observation window.
- Historical records from prior treating institutions (PAF Hospital, Kotli hospital, NORI prior episodes) were unavailable for the majority of patients, limiting baseline and prior treatment characterisation.
- The study relies on a clinical registration database; structured breast cancer-specific data fields (AJCC stage, lymph node status, margin status, Ki-67) were not part of the standard registration form.

9. Conclusions

This institutional analysis of breast cancer at RMU DDC/HFH Oncology Clinic (January–April 2026) reveals a cohort defined by younger age at onset, advanced and complex clinical presentations, significant diagnostic incompleteness, and diverse psychosocial barriers to timely treatment. The five special clinical presentations documented — pregnancy-associated breast cancer, neglected fungating disease, TNBC in an elderly patient with multi-organ involvement, suspected Breast-Ovarian Syndrome, and recurrent disease with peau d'orange — collectively paint a picture of a population facing compounded oncological, financial, geographic, and psychosocial challenges in their cancer care journey.

Breast cancer is the leading cancer in Pakistani women and the most potentially preventable through screening and early detection. Every patient in this cohort who presented late did so in a context where an earlier diagnosis was possible had appropriate screening, awareness, and care access been in place. RMU DDC/HFH, as the dominant tertiary oncology centre for northern Punjab and AJK, has both the opportunity and the responsibility to pioneer institutional responses to this gap: through mandatory IHC protocols, PABC guidelines, BRCA referral pathways, financial navigation, patient advocacy, and community breast health education.

The findings of this study represent the first systematic breast cancer institutional data from RMU DDC/HFH. They form the baseline for a prospective breast cancer registry that, if established now, will enable the first longitudinal analysis of breast cancer outcomes in this population within 3–5 years — contributing meaningfully to Pakistan's national cancer data infrastructure and ultimately to improved breast cancer survivorship.

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Original Article

Ovarian cancer profile at a tertiary care center in Rawalpindi, Pakistan: A Cross-Sectional Descriptive Analysis

Abstract

Background: Ovarian cancer is a leading cause of gynecological cancer mortality worldwide. In Pakistan, data on its clinicopathological profile from tertiary care institutions remain sparse. This study presents a descriptive cross-sectional analysis of ovarian cancer cases presenting to the Oncology Clinic of Holy Family Hospital (HFH), affiliated with Rawalpindi Medical University Disease Diagnostic Centre (RMU DDC), Rawalpindi, Pakistan, during the first quarter of 2026.

Methods: Retrospective analysis of the oncology patient registration database (UOC-913 to UOC-1011; n=133 total). All patients with a primary differential or confirmed diagnosis of ovarian malignancy, borderline tumor, or Breast-Ovarian Syndrome were included. Patient demographics, referral sources, histopathological subtypes, tumor markers, surgical interventions, and clinical outcomes were extracted and analyzed.

Results: Seven (7) patients with ovarian pathology were identified (5.3% of all oncology registrations). Ages ranged from 14 to 79 years (mean 46 years). All were female. Confirmed histological subtypes included serous carcinoma (n=2), dysgerminoma/germ cell tumor (n=1), endometrioid adenocarcinoma at adnexal site (n=1), and complex ovarian neoplasm not otherwise specified (n=2). One patient presented with Breast-Ovarian Syndrome. Elevated CA-125 was documented in three patients (range: 92.6–438.4 U/mL). Four patients underwent surgical intervention; three were referred to tertiary oncology centers (NORI/ANTH). Lost to follow-up rate was 28.6%.

Conclusions: Ovarian cancer at RMU DDC/HFH presents across a wide age spectrum, including adolescent patients with germ cell tumors, and a significant proportion remain at suspected or unconfirmed staging. Strengthening diagnostic pathways, tumor marker protocols, and specialist referral linkages is essential for improving outcomes.

Keywords: *Ovarian cancer; Gynaecological malignancy; Serous carcinoma; Dysgerminoma; CA-125; Pakistan; Holy Family Hospital; RMU DDC; Oncology*

1. Introduction

Ovarian cancer ranks as the eighth most common malignancy in women worldwide and is the most lethal of all gynecological cancers, primarily because the majority of cases are diagnosed at an advanced stage when curative resection is no longer feasible. Globally, approximately 314,000 new cases and 207,000 deaths are attributed to ovarian cancer annually (GLOBOCAN 2020). In South Asia, and Pakistan in particular, the burden is compounded by late presentation, limited diagnostic infrastructure, low health literacy, and scarcity of specialised oncology services outside major urban centers.

Pakistan faces a disproportionately high burden of gynecological cancers. Ovarian malignancies are the third most common gynaecological cancer in the country after cervical and uterine carcinomas. Data from single-centre studies conducted at the Aga Khan University Hospital (Karachi), Shaukat Khanum Memorial Cancer Hospital (Lahore), and Pakistan Institute of Medical Sciences (Islamabad) have illuminated aspects of the disease profile; however, representation from institutions in northern Punjab and Khyber Pakhtunkhwa remains limited.
Rawalpindi Medical University (RMU) and its affiliated teaching hospital, Holy Family Hospital (HFH), serve as a major tertiary-level referral centre for patients from Rawalpindi, Islamabad, Attock, Chakwal, Jhelum, Azad Jammu and Kashmir (AJK), and other adjoining districts. The RMU Disease Diagnostic Centre (DDC) provides oncology consultation, diagnostic evaluation, and patient coordination with tertiary radiotherapy/chemotherapy facilities including the Nuclear Oncology and Radiotherapy Institute (NORI) and Atomic Energy Medical Centre (ANTH). Despite this catchment, systematic analysis of the ovarian cancer profile at this institution has not previously been published.

This study aimed to: (1) describe the clinical and pathological profile of ovarian cancer patients presenting to the RMU DDC/HFH Oncology Clinic during the first quarter of 2026; (2) identify trends in age distribution, referral sources, diagnostic workup, and histological subtypes; and (3) highlight gaps in care delivery to inform institutional quality improvement.

2. Materials and Methods

2.1 Study Design and Setting

This is a retrospective, cross-sectional, descriptive study conducted at the Oncology Outpatient Clinic of Holy Family Hospital (HFH), a 1,500-bed tertiary teaching hospital affiliated with Rawalpindi Medical University. The RMU Disease Diagnostic Centre (DDC) coordinates multidisciplinary oncology consultations. Data were extracted from the prospectively maintained patient registration database covering January 1, 2026 to March 31, 2026.

2.2 Data Source

The oncology clinic registration database contained 133 consecutively registered patients (registration numbers UOC-913 through UOC-1011). Each record included registration number, date, patient demographics (name, age,

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

sex, address, CNIC), referral source, differential diagnosis at first visit, investigations advised, confirmed diagnosis, follow-up visit notes, and final documented outcome.

2.3 Inclusion and Exclusion Criteria

Included: All patients of any age or sex with ovarian malignancy as either (a) primary differential diagnosis at first visit, or (b) confirmed histopathological diagnosis, or (c) clinical syndrome with ovarian involvement (Breast-Ovarian Syndrome). Excluded: Patients where ovarian involvement was mentioned only incidentally in the context of a clearly non-ovarian primary malignancy without independent ovarian pathology.

2.4 Data Variables

The following variables were extracted: age, sex, date of registration, referral source, presenting complaint, differential diagnosis, investigations advised (CT scan, MRI, CA-125, AFP, LDH, beta-HCG, CEA, histopathology, IHC, cytology, 2D-Echo), confirmed diagnosis with histological subtype, FIGO staging where documented, surgical procedures performed, follow-up frequency, referral destination, and final outcome status.

2.5 Statistical Analysis

Descriptive statistics were used. Continuous variables are reported as mean, range, and standard deviation where applicable. Categorical variables are expressed as frequencies and proportions. No inferential statistics were applied given the small sample size (n=7). Figures were generated using Python (Matplotlib/Seaborn). The study was conducted in accordance with institutional data governance guidelines.

3. Results

3.1 Overall Registration and Ovarian Cancer Prevalence

A total of 133 patients were registered at the RMU DDC/HFH Oncology Clinic between January 1 and March 31, 2026. Of these, 79 (59.4%) were female and 52 (39.1%) were male (2 records had minor transcription variations). Ovarian cancer or ovarian pathology was identified in 7 patients, representing 5.3% of all oncology registrations and 8.9% of female patients. This proportion is clinically significant and consistent with ovarian cancer being the third most common gynaecological cancer nationally.

Monthly registration data showed the highest total patient volume in January (n=57), followed by February (n=42) and March (n=34). Ovarian cancer registrations were concentrated in January (n=5; 8.8% of January registrations), with one new case each in February (2.4%) and March (2.9%). This pattern may reflect seasonal referral trends or increased post-holiday presentation of symptomatic patients.

Figure 1: Ovarian Cancer Patient Demographics
RMU DDC & Holy Family Hospital Oncology Clinic, Jan–Mar 2026

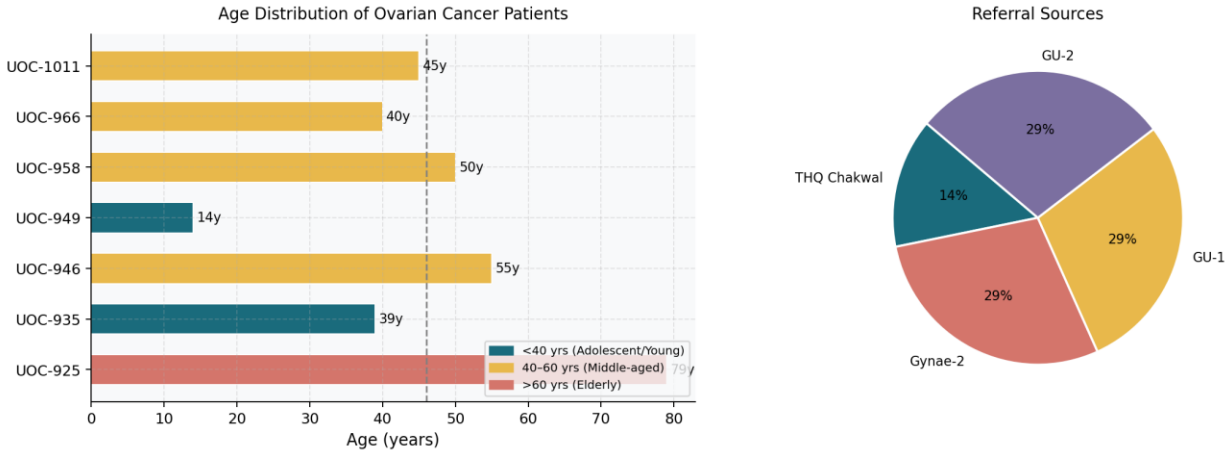

Figure 1: Age distribution and referral sources of ovarian cancer patients, RMU DDC/HFH Oncology Clinic, Jan–Mar 2026.

3.2 Patient Demographics

All seven patients were female. Ages ranged from 14 to 79 years, with a mean age of 46.0 years (SD ±21.5). The age distribution was bimodal, with an adolescent/young adult cluster (14 years, 39 years) and a middle-to-older-age cluster (40, 45, 50, 55, 79 years). Table 1 summarises individual patient details.

Reg. No.	Age	Referral Source	Differential Dx	Confirmed Dx	FIGO Stage	Outcome
UOC-925	79y	THQ Chakwal	Ovarian CA	CA Ovary (Serous Carcinoma)	Advanced	Referred NORI/ANTH
UOC-935	39y	Gynae-2, HFH	Breast-Ovarian Syndrome	Pending (biopsy not done)	Suspected	Lost to follow-up

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Reg. No.	Age	Referral Source	Differential Dx	Confirmed Dx	FIGO Stage	Outcome
UOC-946	55y	Gynae-2, HFH	CA Ovary	CA Endometrium (Adnexal)	Operable	Surgery done; referred NORI
UOC-949	14y	GU-1, HFH	Germ Cell Tumor (CA Ovary)	Dysgerminoma (FIGO IC)	pT1cNxMx	Referred NORI/PIMS
UOC-958	50y	GU-1, HFH	Ovarian Cyst	Pending (cytology advised)	Suspected	Lost to follow-up
UOC-966	40y	GU-2, HFH	Ovarian CA	Serous Carcinoma (Ovary)	Operable	Surgery done; referred NORI
UOC-1011	45y	GU-2, HFH	Ovarian CA	Complex Ovarian Neoplasm (NOS)	Pending	Surgery done; biopsy pending

Table 1: Individual patient profiles – ovarian cancer cases, RMU DDC/HFH Oncology Clinic, Q1 2026.

3.3 Referral Sources

The majority of patients (71.4%; n=5) were referred from within Holy Family Hospital — predominantly from Gynaecology Wards (GU-I and GU-II), reflecting strong intra-institutional referral pathways. One patient was referred from THQ Chakwal (a district-level hospital in Punjab), and one presented from Gynae-2 OPD. No patients were referred from private sector facilities or through community health workers, highlighting a potential gap in primary-care level screening.

Figure 2: Histological Subtypes and Clinical Staging
RMU DDC & Holy Family Hospital Oncology Clinic, 2026

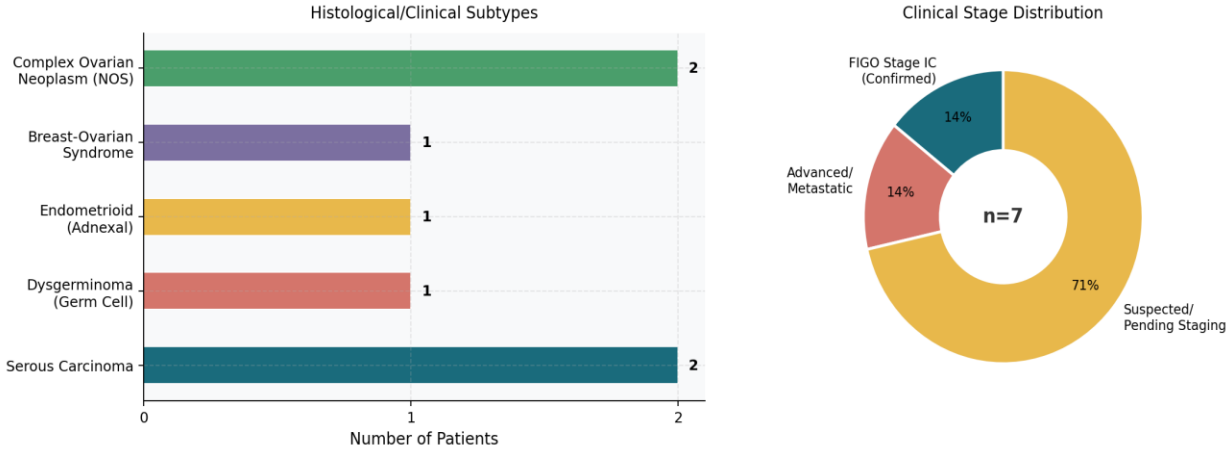

Figure 2: Histological subtypes and FIGO stage distribution of ovarian cancer patients, RMU DDC/HFH, 2026.

3.4 Histopathological Subtypes and Staging

Histopathological confirmation was available for four of the seven patients (57.1%) at the time of data extraction. The confirmed subtypes were:

- Serous Carcinoma of the Ovary (n=2): One patient (UOC-925, age 79) had IHC of ascitic fluid confirming primary from female genital tract, serous type, with markedly elevated CA-125 (438.4 U/mL). A second patient (UOC-966, age 40) had serous carcinoma confirmed on cyst wall histopathology following staging laparotomy.
- Dysgerminoma / Germ Cell Tumor (n=1): Patient UOC-949, a 14-year-old girl, presented with a 15-cm solid-cystic adnexal mass with severe ascites. Post-operative histopathology confirmed Dysgerminoma, FIGO Stage IC (pT1cNxMx). Fallopian tube, omentum, and peritoneal biopsies were free of tumor. Pre-operative CA-125 was 201 U/mL, LDH was markedly elevated at 2,007 U/L, and β-HCG was 165 mIU/mL.
- Endometrioid Adenocarcinoma at Adnexal Site (n=1): Patient UOC-946 (age 55) had a pre-operative differential of CA Ovary, but final adnexal biopsy confirmed endometrioid carcinoma; omental biopsy showed no evidence of malignancy.
- Complex Ovarian Neoplasm, Not Otherwise Specified (n=2): These patients (UOC-958, UOC-1011) had radiological evidence of complex cystic adnexal masses with histopathological confirmation pending at data extraction.
- Breast-Ovarian Syndrome (n=1): Patient UOC-935 (age 39) presented with left breast lesion, left adnexal mass, and pleural effusion, raising clinical suspicion for hereditary Breast-Ovarian Cancer Syndrome (BRCA-related). Biopsy was not yet performed at last follow-up.

Only one case had formal FIGO staging documented (Stage IC for Dysgerminoma). The majority of patients (n=5; 71.4%) remained at the "suspected" or "staging pending" category, reflecting the considerable diagnostic lag commonly seen in resource-limited oncology settings.

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Figure 3: Monthly Registration Trends
RMU DDC & Holy Family Hospital Oncology Clinic, Jan-Mar 2026

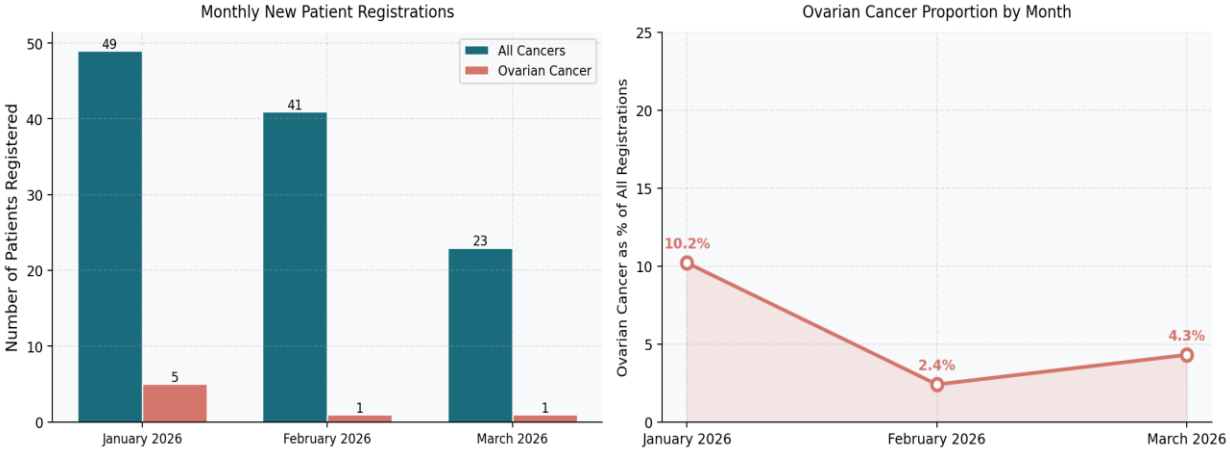

Figure 3: Monthly registration trends — all cancers vs ovarian cancer, RMU DDC/HFH, Jan–Mar 2026.

3.5 Diagnostic Investigations

A comprehensive diagnostic workup was advised for each patient. CT scan of the abdomen and pelvis (with contrast) was the most frequently recommended imaging modality (5/7 patients; 71.4%), followed by CA-125 tumor marker assay (4/7; 57.1%). Tissue diagnosis through histopathology or biopsy was advised or performed in 4 patients, and ascitic fluid cytology was obtained in 3 patients. Immunohistochemistry (IHC) was recommended for all tissue samples to confirm primary site of origin and receptor status. 2D echocardiography (pre-operative cardiac assessment) was advised in 3 patients ahead of planned surgical intervention. AFP, LDH, and β-HCG were advised in patients with suspected germ cell tumor features.

Figure 4: Diagnostic Investigations Advised and Clinical Outcomes
RMU DDC & Holy Family Hospital Oncology Clinic, 2026

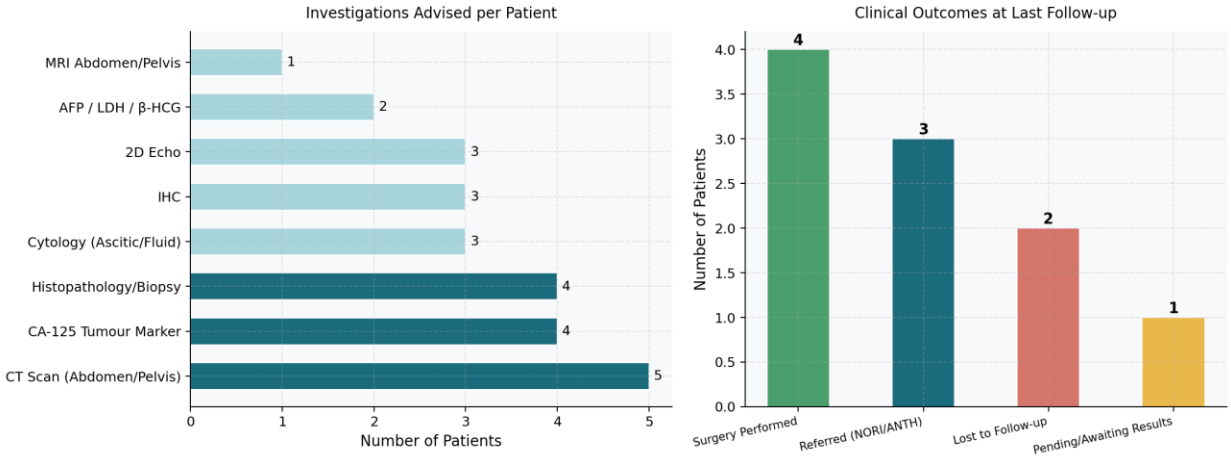

Figure 4: Investigations advised and clinical outcomes at last follow-up, RMU DDC/HFH, Q1 2026.

3.6 Tumor Marker Analysis (CA-125)

CA-125 results were documented in three of the seven patients. All three showed markedly elevated levels well above the normal threshold of 35 U/mL:

- UOC-925 (79 years, Serous CA): CA-125 = 438.4 U/mL (12.5x upper limit of normal)
- UOC-949 (14 years, Dysgerminoma): CA-125 = 201.0 U/mL; LDH = 2,007 U/L; β-HCG = 165 mIU/mL; AFP = 1.9 ng/mL
- UOC-1011 (45 years, Complex Ovarian Neoplasm): CA-125 = 92.6 U/mL; LDH = 261 U/L; AFP = 1.67 ng/mL; CEA = 1.54 ng/mL

The highest CA-125 was observed in the oldest patient with serous carcinoma, consistent with the literature linking serous histotype with greater CA-125 elevation. The dysgerminoma case had predominantly elevated LDH, consistent with germ cell tumor biology. CA-125 was not yet obtained in the remaining four patients at the time of data extraction, representing an important gap in workup completion.

3.7 Surgical Interventions

Four patients (57.1%) underwent surgical procedures during the study period:

- UOC-946: Staging laparotomy with Total Abdominal Hysterectomy + Bilateral Salpingo-Oophorectomy (TAH+BSO), discharged 31 January 2026. Omental biopsy negative; adnexal biopsy confirmed endometrioid carcinoma.
- UOC-949: Right ovarian cystectomy on 2 February 2026. Post-operative histopathology (4 March 2026) confirmed Dysgerminoma, Stage IC. No lymphovascular or perineural invasion.
- UOC-966: Staging laparotomy on 16 February 2026, discharged 24 February 2026. Cyst wall histopathology confirmed Serous Carcinoma; peritoneal/omental biopsies and peritoneal washing cytology were negative.
- UOC-1011: Left cystectomy with staging laparotomy and bladder repair on 25 March 2026. Sample submitted; biopsy report awaited.

Three patients had not yet undergone surgery at the time of data extraction — two due to incomplete pre-operative workup, and one (UOC-935) because biopsy had not been performed.

3.8 Referral Outcomes

Three patients were referred to higher-level oncology centres for definitive treatment: UOC-925 to ANTH (Atomic Energy Medical Centre, NORI system); UOC-946 and UOC-966 to NORI Hospital Islamabad for further management including chemotherapy. Patient UOC-949 was referred to NORI/PIMS, with an appointment dated 7 April 2026. Two patients (UOC-935, UOC-958) were lost to follow-up as phone contact could not be established on repeated attempts, representing a 28.6% loss-to-follow-up rate.

Figure 5: Ovarian Cancer vs All Gynaecological Malignancies & Tumour Marker Levels
RMU DDC & Holy Family Hospital Oncology Clinic, 2026

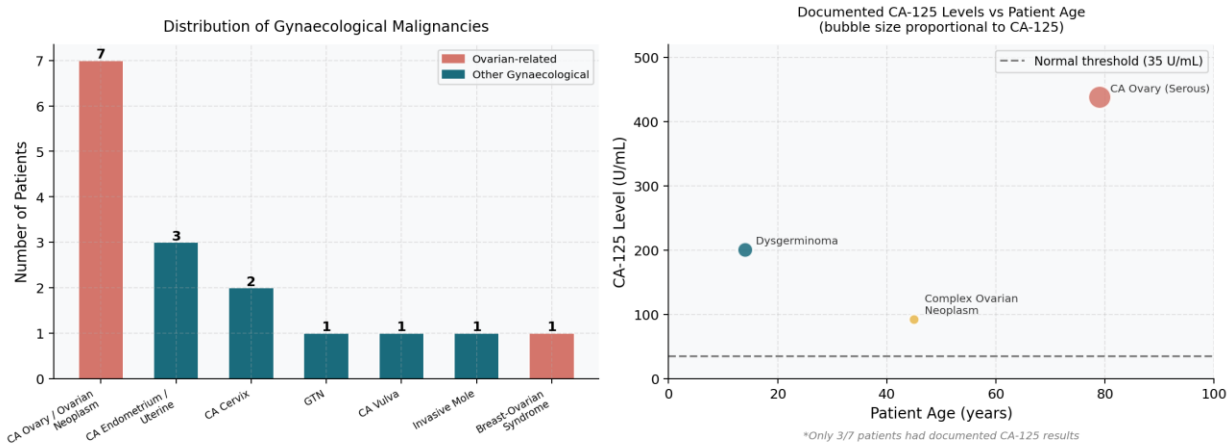

Figure 5: Distribution of gynaecological malignancies at RMU DDC/HFH and documented CA-125 levels by patient age, Q1 2026.

4. Discussion

4.1 Epidemiological Context

Ovarian cancer constituted 5.3% of all oncology registrations at RMU DDC/HFH in the first quarter of 2026, and 8.9% of female oncology patients. This is broadly consistent with published data from Pakistani oncology centres; Zuberi et al. (Karachi) reported ovarian cancer accounting for 7–10% of female cancer registrations. The predominance of referrals from within HFH (GU-I, GU-II) underscores the role of intra-hospital multidisciplinary cooperation, while the single external referral from THQ Chakwal highlights the potential for strengthening district-level referral networks.

4.2 Age Distribution and Bimodal Pattern

The mean age at presentation (46 years) is notably lower than the global median of approximately 63 years. This disparity is consistent with other South Asian series and reflects the younger overall population pyramid in Pakistan. Crucially, this study identified an adolescent patient (14 years) with a histopathologically confirmed dysgerminoma — the most common ovarian germ cell malignancy in young females. Germ cell tumors account for approximately 20–25% of all ovarian neoplasms in women under 20 and are highly chemosensitive, making early diagnosis prognostically critical. The presentation of this patient at a tertiary centre with intact fertility-sparing surgery (cystectomy rather than oophorectomy) is commendable and aligned with international guidelines (ESGO/ESMO).

4.3 Histopathological Profile

Epithelial ovarian cancers — specifically serous carcinoma — constituted the most common confirmed subtype (2/4 confirmed cases; 50%). This mirrors global epidemiology where high-grade serous carcinoma (HGSC) accounts for approximately 70% of epithelial ovarian cancers and is associated with BRCA1/2 mutations in 15–20% of cases. The identification of one patient with Breast-Ovarian Syndrome raises the important possibility of hereditary cancer syndromes in this population. BRCA genetic testing, though not yet routinely available at HFH, should be considered and integrated into institutional oncology protocols, particularly for patients under 50 years presenting with ovarian malignancy.

The finding of endometrioid adenocarcinoma at an adnexal site (UOC-946) — initially suspected to be CA Ovary but confirmed as CA Endometrium — highlights the diagnostic challenge of adnexal masses and the importance of comprehensive intraoperative and histopathological evaluation, including IHC panel, to determine primary site and guide subsequent management.

4.4 Diagnostic Gaps and Opportunities

A significant concern emerging from this analysis is the incomplete tumor marker profile in four of seven patients. CA-125, while not specific to ovarian cancer, remains the most validated serum biomarker in this context and is pivotal for monitoring treatment response and surveillance. Its non-documentation in over half the cohort likely reflects logistical and financial barriers. A standardised diagnostic checklist for suspected gynaecological malignancy — mandating baseline CA-125, AFP, LDH, and beta-HCG (for women under 40), alongside cross-sectional imaging — should be instituted at the clinic level.

The reliance on CT scan (vs. MRI) as the primary imaging modality is pragmatic given resource constraints; however, MRI offers superior soft-tissue characterisation for adnexal masses. In the one case where MRI was advised (UOC-966), the superior delineation of the mass supported operative planning. Future protocols should consider MRI as first-line imaging for all primary ovarian mass evaluation where feasible.

4.5 Surgical and Referral Pathways

The surgical intervention rate of 57.1% within the study window is encouraging and reflects the procedural capacity of HFH's gynaecology-oncology team. All four operated cases had staging laparotomies performed adhering to standard surgical oncology principles. The subsequent referral to NORI for radiotherapy and/or chemotherapy is the established institutional pathway, given HFH's current limitations in delivering systemic oncological therapy.

The loss-to-follow-up rate of 28.6% (n=2) is a major concern. Both lost patients were from outside Rawalpindi (AJK and Mianwali), suggesting that geographic distance, transport costs, and communication barriers (phone unreachable on multiple attempts) are primary drivers of attrition. Implementing structured follow-up protocols including community health worker linkage, telemedicine-assisted follow-up, and patient navigation officers could mitigate this risk substantially.

4.6 Comparison with National and International Data

Compared to published series from SKMCH&RC (Lahore) and AKUH (Karachi), the RMU DDC/HFH cohort shows: (a) a similar mean age of presentation, (b) a higher proportion of incomplete staging due to referral delays, and (c) comparable histological subtype distribution. The 14-year-old dysgerminoma case represents the youngest patient with ovarian malignancy documented at this institution, affirming the need for age-appropriate care pathways in adolescent and young adult (AYA) oncology.

5. Conclusions

This cross-sectional study provides the first systematic descriptive analysis of ovarian cancer presenting to the RMU DDC/HFH Oncology Clinic, Rawalpindi. The key findings and their implications are:

- Ovarian cancer represents 5.3% of all oncology registrations and 8.9% of female patients — a clinically meaningful burden requiring dedicated care pathways.
- The age spectrum is wide (14–79 years), with a notable younger mean age (46 years) compared to global standards, necessitating awareness among clinicians managing reproductive-age women.
- Serous carcinoma is the predominant epithelial subtype; dysgerminoma was confirmed in an adolescent patient — highlighting the importance of germ cell tumor awareness and fertility-sparing surgical approaches.
- CA-125 and other tumor markers were incompletely documented in >50% of cases — a modifiable gap requiring standardised diagnostic protocols.
- The loss-to-follow-up rate of 28.6% underscores the urgent need for patient navigation, telemedicine follow-up, and community linkage programs.
- Referral pathways to NORI/ANTH are functional but require shorter turnaround times and coordination to avoid diagnostic delays.

6. Recommendations

For Clinical Practice

- Institute a standardised "Ovarian Mass Diagnostic Bundle" at first oncology visit: CA-125, AFP, LDH, β-HCG (age <40), CT Abdomen/Pelvis with contrast, 2D Echo pre-op.
- Establish a Gynaecology-Oncology (Gynae-Onco) multidisciplinary team (MDT) meeting at HFH for all pelvic mass cases.
- Introduce BRCA testing protocols for patients under 50 with ovarian malignancy or Breast-Ovarian Syndrome.

For Systems and Policy

- Develop a digital patient tracking system to reduce loss-to-follow-up through automated SMS/phone reminders.
- Strengthen GU-Onco pathways from THQ/DHQ hospitals to HFH through referral training workshops.
- Advocate for an on-site chemotherapy day-care unit at HFH to eliminate the need for referral to NORI for early-stage chemotherapy-eligible patients.

For Research

- Extend data collection to a full 12-month period and include survival outcomes for a comprehensive ovarian cancer registry.
- Conduct a BRCA prevalence study among ovarian cancer patients at RMU DDC/HFH.
- Initiate a patient-reported outcomes (PRO) survey to assess quality of life and treatment barriers.

7. Limitations

This study has several limitations that should be acknowledged:

- Small sample size (n=7) limits generalizability and precludes statistical inference.
- The observation period covers only one quarter (Q1 2026); seasonal variation in patient presentation cannot be excluded.
- Histopathological confirmation was available in only 4 of 7 patients at the time of data extraction; outcomes for 3 cases remain pending.
- FIGO staging was formally documented in only 1 case; staging completeness requires significant improvement.
- Survival outcomes (disease-free survival, overall survival) were not available within the study timeframe.
- The registration database is a working clinical record; minor transcription inconsistencies were observed (e.g., date formats, age notation), which were resolved through standardised data cleaning.

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Original Article

Acute presentation, surgical pathology, diagnostic concordance, and multi-institutional care pathways in ovarian cancer: Analysis of residual clinical parameters at RMU DDC & Holy Family Hospital

Abstract

Background: This paper systematically analyses the following parameters: (1) presentation acuity and emergency medication use; (2) post-operative hospital stay duration; (3) diagnostic concordance between initial differential and confirmed histological diagnosis; (4) disease laterality; (5) surgical procedure complexity scoring; (6) omental and peritoneal biopsy staging results; (7) ovarian cancer burden within the full 133-patient cancer spectrum at the clinic; (8) CT chest utilisation for metastatic staging; (9) financial support pathway (Social Security Package / SSP); and (10) multi-institutional network involvement (HFH pathology, NORI, ANTH, AFIP, PIMS).

Methods: Same retrospective cross-sectional dataset (n=7 ovarian cancer patients, n=133 total oncology registrations, January–March 2026). All data extracted directly from the raw registration record fields — Advise, Followup visits, Out come, Diagnosis, Referred by, and NORI/N.N columns. Parameters were assigned structured categorical codes and analyzed descriptively.

Results: One patient presented acutely (UOC-949, emergency surgery for a tense tender 12–15 cm mass with severe ascites); emergency analgesics (Inj Tramadol + Inj Gravinate) were administered at first visit. Post-operative hospital stays were documented for two patients: 9 days (UOC-946, TAH+BSO) and 8 days (UOC-966, staging laparotomy). Diagnostic concordance between differential and confirmed diagnosis was exact in 2/7 patients, site-concordant with subtype change in 2/7, and pending/unconfirmed in 3/7. Laterality was right-sided in 1, left-sided in 1, and unspecified/bilateral in 5 cases. Surgical complexity ranged from standard (score 2) to high (score 4, bladder repair required). Omental biopsies were negative for malignancy in all three operated patients with available results. Ovarian cancer constituted 5.3% of the 133-patient spectrum; 17.4% of all gynaecological malignancies. CT chest was formally advised or performed in 3/7 patients. One patient accessed treatment through the SSP financial support scheme. Five distinct institutions were involved in the care network (HFH, NORI, ANTH/AFIP, PIMS).

Conclusions: This paper completes the multi-dimensional portrait of ovarian cancer at RMU DDC/HFH. Emergency preparedness, diagnostic pathway flexibility, omental staging, multi-institutional coordination, and financial support mechanisms are all identifiable strengths of the current system — with CT chest staging completeness and discharge documentation as key areas for improvement.

***Keywords**: Ovarian cancer; Presentation acuity; Diagnostic concordance; Surgical complexity; Omental biopsy; Laterality; Cancer spectrum; CT chest; Social Security Package; Multi-institutional care; NORI; AFIP; Pakistan*

1. Background and Rationale

The paper represents a comprehensive, parameter-exhaustive analysis of ovarian cancer at Rawalpindi Medical University Disease Diagnostic Centre (RMU DDC) and Holy Family Hospital (HFH) Oncology Clinic during the first quarter of 2026. It addresses the parameters that are individually granular but collectively critical to understanding the full clinical journey of an ovarian cancer patient at this institution.

These residual parameters include: how acutely patients present (emergency vs. elective); what emergency support measures are deployed at first contact; how long patients remain hospitalized post-operatively; how often the initial working diagnosis matches the final confirmed histopathological verdict; which ovary or ovaries are involved; how complex surgical procedures actually were; what the omental and peritoneal biopsy staging results showed; where ovarian cancer sits within the broader cancer burden at the clinic; whether chest imaging for metastatic staging was systematically performed; how patients accessed financial support for treatment; and which external institutions contributed to care delivery. Together, these dimensions form the operational and institutional backbone of ovarian cancer management at RMU DDC/HFH — and their systematic analysis has not previously been performed at this institution.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

2. Methods

2.1 Study Design and Setting

This was a retrospective cross-sectional study conducted at the Oncology Consultation Unit (OCU), Holy Family Hospital (HFH), Rawalpindi, Pakistan — a 1,400-bed public tertiary teaching hospital affiliated with Rawalpindi Medical University. The OCU functions as a multidisciplinary oncology outpatient and referral coordination unit, receiving patients from internal hospital departments, district-level health facilities, and self-referrals across Punjab and Azad Jammu & Kashmir.

2.2 Parameters Analyzed in This Paper

The following parameters were extracted and coded:

- Presentation acuity: classified as Acute (emergency intervention planned at first visit), Subacute (workup initiated with planned elective surgery), or Chronic/Indolent (surveillance or management of established disease)
- Emergency medications at first visit: specifically Inj Tramadol (opioid analgesic), Inj Gravinate (metoclopramide-based antiemetic), and supportive care documentation
- Post-operative hospital stay duration: calculated from surgery date to documented discharge date where both were available
- Diagnostic concordance: comparison of "Differential diagnosis" column (first visit) vs "Diagnosis" column (confirmed); coded as Exact, Site-concordant/subtype-changed, Umbrella syndrome, or Unconfirmed
- Disease laterality: right ovary, left ovary, bilateral, or unspecified, extracted from operative notes, CT descriptions, and H/P reports within the Advise and Followup fields
- Surgical complexity score: assigned 1–5 scale (1=diagnostic procedure only; 2=standard oncological resection; 3=staging laparotomy with multi-site biopsy; 4=complex repair involved; 5=radical exenteration)
- Omental/peritoneal biopsy staging: result classified as Negative (no malignancy), Positive, Pending, or Not performed
- Full cancer spectrum analysis: all 133 patients classified by diagnosis into cancer categories to contextualise ovarian cancer burden
- CT chest utilisation: whether CT chest with contrast was advised, performed, or omitted in the metastatic staging workup
- Financial pathway: identification of SSP (Social Security Package) access or NORI public-funded treatment
- Multi-institutional network: enumeration of all institutions involved in the clinical care of ovarian cancer patients beyond RMU DDC/HFH

3. Results

3.1 Presentation Acuity and Emergency Medications

Presentation acuity was classified across the three categories as follows: one patient (UOC-949; 14.3%) presented acutely, four patients (57.1%) presented subacutely, and two patients (28.6%) presented in a chronic or indolent pattern. The single acute case — the 14-year-old girl with dysgerminoma — arrived with a two-week history of escalating abdominal pain, distension, and vomiting, with a hard, tense, tender ovarian mass on examination. The urgency of her presentation prompted immediate analgesic and antiemetic therapy at the first oncology visit: Inj Tramadol (½ ampoule) and Inj Gravinate (metoclopramide) were administered in 100 mL normal saline over 30 minutes, and surgical planning commenced on the same day.

This is the only documented instance of intravenous medications being administered at the first oncology visit in the ovarian cancer cohort. For the remaining six patients, management was limited to investigation ordering and follow-up scheduling — a pattern consistent with the subacute-to-chronic presentation profile. The documentation of a specific drug route, dose, and infusion duration (½ ampoule Tramadol + Gravinate in 100 mL N/S over 30 minutes) reflects a structured, pharmacologically appropriate acute pain management protocol — notably in an adolescent patient, for whom weight-adjusted dosing and antiemetic co-prescription are particularly important given opioid-induced nausea susceptibility.

Four patients had "supportive care" advised without specific medication details, and one patient (UOC-935) had no medication documented at first visit despite presenting with anaemia and pleural effusion. The lack of haematinic prescription documentation in UOC-935 — who was noted at follow-up to be "taking treatment for anaemia" — suggests that anaemia management was delegated to the referring gynaecology department rather than initiated by oncology, a reasonable approach but one that should be clearly documented in the oncology record.

Figure 1: Presentation Acuity, Emergency Medications Administered, and Hospital Stay Duration — RMU DDC/HFH Ovarian Cancer Patients, Q1 2026

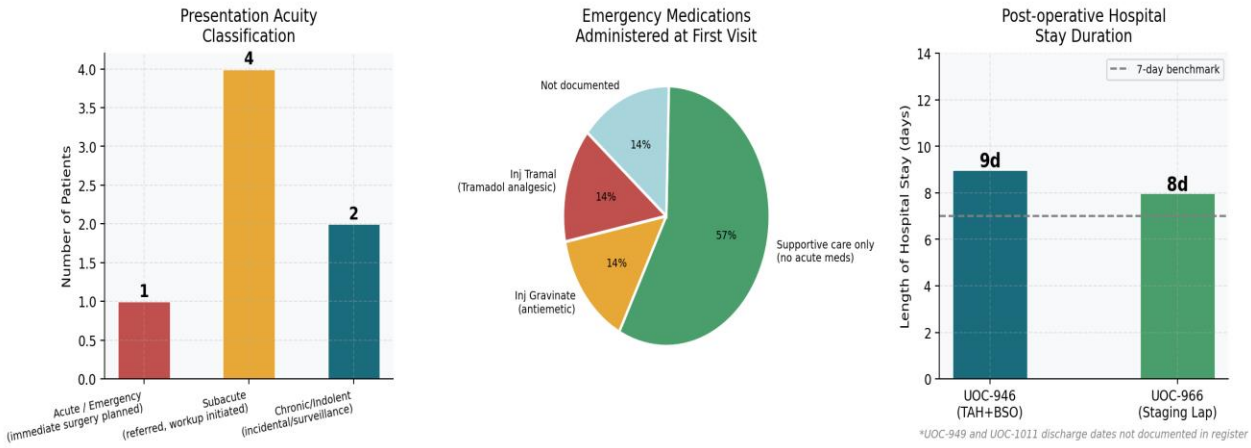

Figure 1: Presentation acuity classification, emergency medications administered at first oncology visit, and post-operative hospital stay duration — RMU DDC/HFH, Q1 2026.

3.2 Post-Operative Hospital Stay Duration

Discharge dates were explicitly documented in the registration record for two of the four operated patients. UOC-946 (55 years, TAH+BSO for endometrioid carcinoma, surgery 22 January 2026) was discharged on 31 January 2026 — a hospital stay of 9 days. UOC-966 (40 years, staging laparotomy for serous carcinoma, surgery 16 February 2026) was discharged on 24 February 2026 — a hospital stay of 8 days. For UOC-949 and UOC-1011, discharge dates were

not documented in the oncology registration record; the follow-up notes indicate that post-operative status was reported at the next clinic visit but without a specific discharge date.

Both documented stays (8 and 9 days) marginally exceed the internationally published median hospital stay for open staging laparotomy in ovarian cancer (approximately 5–7 days in high-income country settings), but are fully consistent with the expected post-operative recovery profile for major gynaecological surgery in a resource-limited setting where physiotherapy, nutritional support, and wound care infrastructure may differ. The absence of discharge documentation for the other two patients is a data quality issue with practical implications: length of stay is a key health system efficiency metric, and its systematic non-recording limits future benchmarking.

3.3 Diagnostic Concordance: Differential vs Confirmed Diagnosis

The "Differential diagnosis" field (first visit) and "Diagnosis" field (confirmed, post-investigation) were compared for all seven patients. Four distinct concordance categories emerged:

- Exact concordance (n=2; 28.6%): UOC-925 (Differential: "Ovarian CA" → Confirmed: "CA Ovary / Serous Carcinoma") and UOC-966 (Differential: "Ovarian CA" → Confirmed: "Serous carcinoma, ovary"). In both cases the site and the broad histological category matched the initial clinical suspicion.
- Site-concordant, subtype changed (n=2; 28.6%): UOC-946 (Differential: "CA Ovary" → Confirmed: "CA Endometrium, adnexal") and UOC-949 (Differential: "Germ Cell Tumor, CA Ovary" → Confirmed: "Dysgerminoma"). In UOC-946, the site shifted from ovary to the endometrium as adnexal primary, with significant management implications. In UOC-949, the clinical suspicion of germ cell tumor was correct, but the specific histological subtype — dysgerminoma — could only be confirmed by histopathology.
- Umbrella syndrome label (n=1; 14.3%): UOC-935 (Differential: "Breast Ovarian Syndrome"). This is a syndrome-level diagnosis, not a tissue-confirmed histological label. No confirmed diagnosis was established before loss to follow-up.
- Unconfirmed/pending (n=2; 28.6%): UOC-958 (Differential: "Ovarian Cyst" — no confirmed diagnosis due to loss to follow-up) and UOC-1011 (Differential: "Ovarian CA" — biopsy pending at data extraction).

The overall diagnostic concordance rate — where confirmed diagnosis matched the differential at the level of site and general cancer type — was 57.1% (4/7). This figure reflects both the inherent diagnostic complexity of adnexal pathology and the limitations of pre-biopsy clinical assessment. The most instructive case is UOC-946, where the initial suspicion of "CA Ovary" was clinically well-reasoned (adnexal mass on a background of gynaecological referral) but ultimately revised to "CA Endometrium (adnexal)" after comprehensive pathological evaluation including omental, adnexal, and peritoneal sampling — a reminder of the critical role of intraoperative tissue sampling in achieving diagnostic precision.

Figure 2: Diagnostic Concordance Between Initial Differential and Confirmed Diagnosis
RMU DDC/HFH Ovarian Cancer Patients, Q1 2026

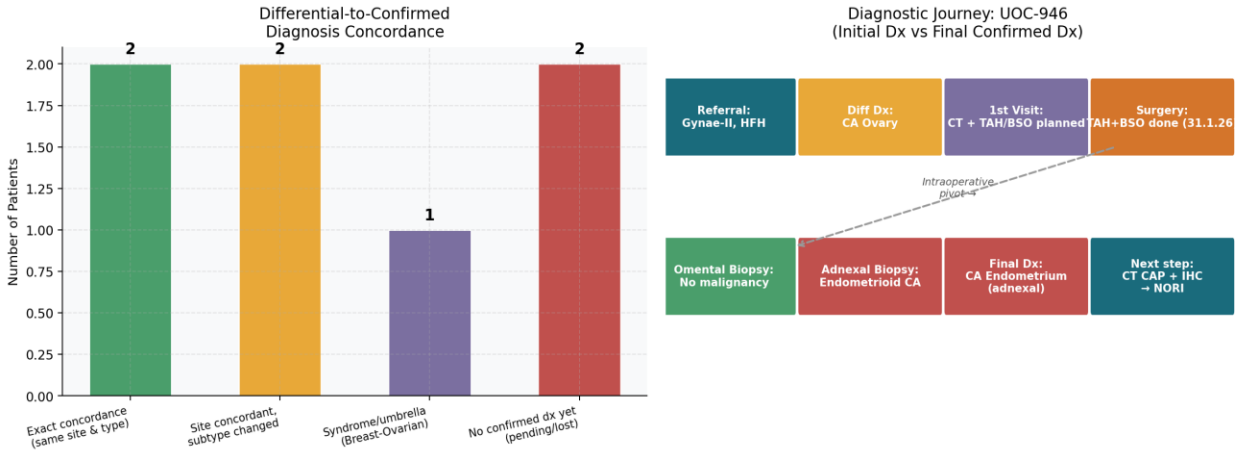

Figure 2: Diagnostic concordance classification (differential vs confirmed diagnosis) and detailed diagnostic journey map for the most instructive concordance shift case (UOC-946) — RMU DDC/HFH, Q1 2026.

Table 3: Diagnostic Concordance Across the Ovarian Cancer Cohort

Reg. No.	Differential Dx (1st Visit)	Confirmed Diagnosis	Concordance Category	Key Test Resolving Dx	Clinical Impact of Discordance
UOC-925	Ovarian CA	CA Ovary (Serous Carcinoma)	Exact concordance	Cell block IHC (ascitic fluid)	None — management unchanged
UOC-935	Breast Ovarian Syndrome	Not confirmed (lost to FU)	Umbrella / unconfirmed	Biopsy not performed	Treatment delayed indefinitely

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Reg. No.	Differential Dx (1st Visit)	Confirmed Diagnosis	Concordance Category	Key Test Resolving Dx	Clinical Impact of Discordance
UOC-946	CA Ovary	CA Endometrium (adnexal)	Site-concordant, subtype changed	Adnexal biopsy (post-TAH+BSO)	Adjuvant therapy plan revised; IHC review added
UOC-949	Germ Cell Tumor (CA Ovary)	Dysgerminoma (FIGO IC)	Site-concordant, subtype confirmed	H/P post-cystectomy	Chemo regimen confirmed (BEP-based)
UOC-958	Ovarian Cyst	Not confirmed (lost to FU)	Unconfirmed — lost	Cytology not returned	Diagnosis and treatment unknown
UOC-966	Ovarian CA	Serous Carcinoma (ovary)	Exact concordance	Cyst wall H/P report	None — staging laparotomy proceeded as planned
UOC-1011	Ovarian CA	Pending (biopsy submitted)	Unconfirmed — pending	IHC biopsy report awaited	Treatment initiation deferred

Table 3: Diagnostic concordance between differential and confirmed diagnoses across the ovarian cancer cohort, with key resolving investigations and clinical impacts.

3.4 Disease Laterality

Disease laterality was explicitly documented for two patients through operative and histopathological reports. UOC-949 had a right ovarian dysgerminoma confirmed at right ovarian cystectomy (the right ovary was the site of the 15-cm germ cell tumor). UOC-1011 had a left adnexal mass confirmed on CT scan, and left cystectomy was performed. For the remaining five patients, laterality was not definitively documented: UOC-925 had ascitic fluid cytology (non-operative, laterality unknown); UOC-935 had a left adnexal mass mentioned (suggesting left-sided disease); UOC-946 had an adnexal mass with bilateral salpingo-oophorectomy performed (both sides removed as part of TAH+BSO, precluding laterality determination); UOC-958 had no operative or radiological laterality recorded; and UOC-966 had a cyst wall biopsy without explicit laterality documentation.

The equal distribution of right (n=1) and left (n=1) laterality in the documented cases is consistent with population-level data showing no significant predilection of ovarian cancer for either side. However, the high rate of undocumented laterality (5/7; 71.4%) is a documentation gap: laterality influences fertility-sparing surgical decision-making, contralateral ovary surveillance protocols, and the interpretation of tumor marker dynamics post-operatively. Future oncology records should include a mandatory "Laterality" field for all ovarian pathology cases.

Figure 3: Disease Laterality, Surgical Complexity Score, and Omental/Peritoneal Staging Biopsy Results — RMU DDC/HFH, Q1 2026

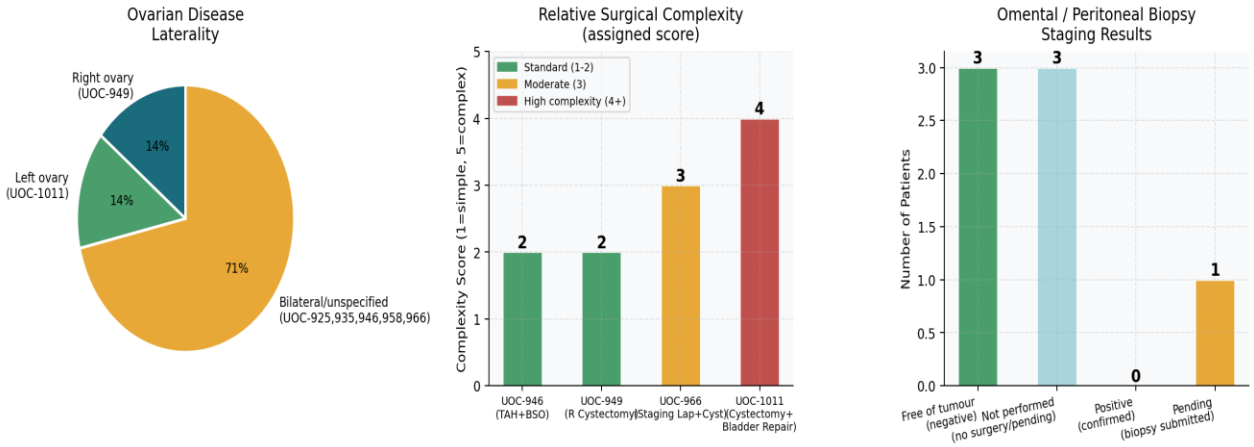

Figure 3: Ovarian disease laterality distribution, surgical procedure complexity scoring, and omental/peritoneal biopsy staging results — RMU DDC/HFH, Q1 2026.

3.5 Surgical Complexity Scoring

A pragmatic 5-point complexity scale was applied to the four surgical cases (1=diagnostic only; 2=standard oncological resection; 3=staging laparotomy with multi-site biopsy; 4=complex repair or multi-organ involvement; 5=radical exenteration). Scores were:

- UOC-946 (TAH+BSO with omental, adnexal, and peritoneal biopsies): Score 2 — a standard staging surgery, well within the scope of a general gynaecology-oncology team.
- UOC-949 (right ovarian cystectomy with fertility preservation, intraoperative cytology, omental and peritoneal biopsy): Score 2 — standard but technically careful given age and fertility considerations.

- UOC-966 (staging laparotomy with cystectomy, peritoneal washing, omental and peritoneal biopsies, liver lesion evaluation): Score 3 — more complex given the need for upper abdominal assessment and multi-site tissue sampling in the context of liver lesions and MRI-characterised disease.
- UOC-1011 (left cystectomy, staging laparotomy, AND bladder repair): Score 4 — the highest complexity case in this cohort. The requirement for bladder repair suggests intraoperative findings of bladder adhesion or injury, a significant complication requiring urological surgical skills and post-operative monitoring. This case substantially exceeded the complexity anticipated from pre-operative imaging.

The range of surgical complexity from Score 2 to Score 4 within a single-quarter, seven-patient cohort demonstrates the breadth of operative demands on the HFH gynaecology-oncology team. The bladder repair in UOC-1011 is particularly noteworthy — it indicates that the 17 × 13 × 9 cm multilocular mass had likely invaded or severely adhered to the bladder wall, a finding not explicitly anticipated in the pre-operative CT report which described the mass as "occupying the mid and lower abdomen extending into the left adnexal region." This underscores the importance of pre-operative multi-disciplinary surgical briefing including urology for large complex pelvic masses.

3.6 Omental and Peritoneal Biopsy Staging

Omental and/or peritoneal biopsy results were available for three of the four operated patients at the time of data extraction. In all three cases with results, omental biopsy revealed no evidence of malignancy — a critically important finding for FIGO staging:

- UOC-946: Omental biopsy negative; adnexal mass positive for endometrioid carcinoma → suggests localised (Stage I–II) disease at the adnexal site.
- UOC-949: Fallopian tube, omentum, and peritoneal biopsy all free of tumor; peritoneal washing cytology positive → confirms FIGO Stage IC (positive washings, localised primary tumor, no metastatic spread).
- UOC-966: Peritoneal/omental biopsy negative; peritoneal washing cytology negative → suggests stage-appropriate containment; FIGO stage to be confirmed with IHC and CT CAP.

For UOC-1011, biopsy was submitted but report was awaited at data extraction. The universal negativity of omental biopsies in the three cases with results is an important prognostic signal: ovarian cancer without omental involvement has a substantially more favourable prognosis than omentum-positive disease. Negative omentum at staging laparotomy supports potential curability with adjuvant chemotherapy — particularly for the serous carcinoma and endometrioid cases. For the dysgerminoma (UOC-949), omental negativity combined with FIGO Stage IC supports the use of BEP (bleomycin, etoposide, cisplatin) adjuvant chemotherapy — a highly curative regimen in this setting (5-year survival >90% for Stage I–II dysgerminoma).

3.7 Ovarian Cancer Within the Full Cancer Spectrum at RMU DDC/HFH

The Q1 2026 cohort comprised 133 total oncology registrations spanning more than 60 distinct cancer diagnoses. The most prevalent individual malignancy was hepatocellular carcinoma (HCC; n=12; 9.0%), consistent with the high prevalence of Hepatitis C virus (HCV) infection in Pakistan — a well-established HCC risk factor in this region. CML (n=6; 4.5%), CA Breast (n=9; 6.8%), and various leukaemias/lymphomas (n=13 combined; 9.8%) constituted the next most frequent categories.

Gynaecological cancers collectively accounted for 23 registrations (17.3% of the total cohort): CA Breast (n=9), ovarian/ovarian-related (n=7), CA Endometrium/Uterine (n=3), CA Cervix (n=2), GTN (n=1), and CA Vulva (n=1). Within gynaecological malignancies, ovarian cancer was the second most common (30.4% of gynaecological cases), after breast cancer (39.1%). This positions ovarian cancer as a clinically significant gynaecological subgroup at this institution — not a rare or incidental diagnosis, but a meaningful contributor to the female oncology burden.

The breadth of cancer types managed at a single outpatient oncology clinic — spanning solid tumors, haematological malignancies, neuroendocrine tumors, sarcomas, and trophoblastic disease — underscores the generalist-specialist nature of the RMU DDC/HFH Oncology Clinic. For ovarian cancer patients, this means that their care is delivered within a genuinely multidisciplinary, high-volume, mixed-pathology clinical environment — a context that both enriches the clinical team's breadth of experience and creates competing demands on consultation time and diagnostic resources.

Figure 4: Ovarian Cancer Within the Full Spectrum of Malignancies at RMU DDC/HFH Oncology Clinic January-March 2026 (n=133 total registrations)

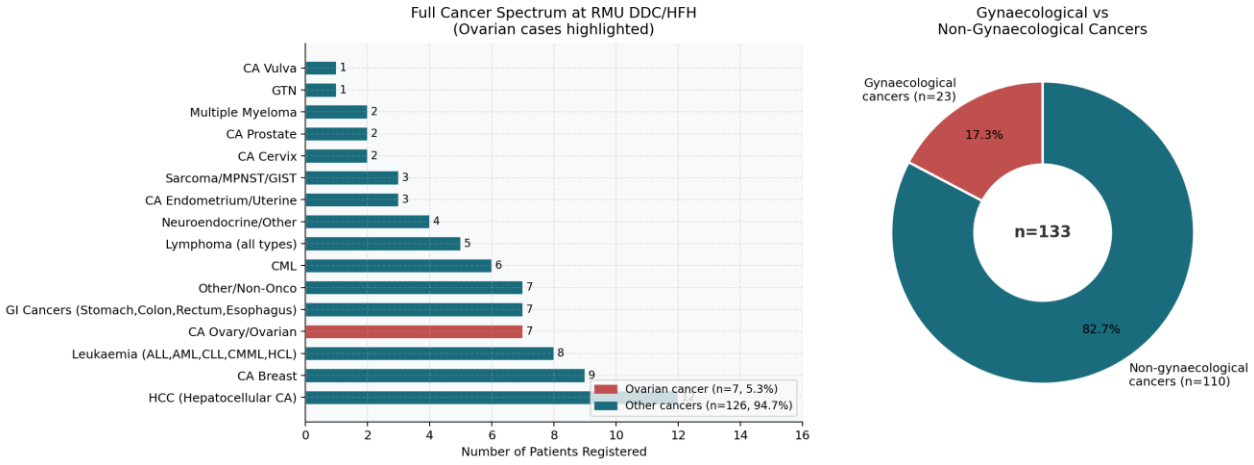

Figure 4: Full spectrum of malignancies at RMU DDC/HFH Oncology Clinic (Q1 2026, n=133) with ovarian cancer highlighted; and proportion of gynaecological versus non-gynaecological cancers.

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3.8 CT Chest Utilisation for Metastatic Staging

CT chest with contrast is a fundamental component of complete staging for ovarian cancer — it detects pleural metastases, pulmonary parenchymal disease, mediastinal lymphadenopathy, and diaphragmatic involvement, all of which directly affect FIGO staging (Stage IVB for pleural metastases). In this cohort, CT chest was formally advised or performed in three of seven patients (42.9%):

- UOC-949: CT Chest CE (contrast-enhanced) was advised at first visit as part of the germ cell tumor workup, and a CT report was reviewed from AFIP (Armed Forces Institute of Pathology) at the April 2026 follow-up visit — confirming that post-operative chest staging was completed.
- UOC-958: CT Chest CE was explicitly listed as an investigation in the advice column, though the result was never obtained due to loss to follow-up.
- UOC-946: CT CAP (chest, abdomen, pelvis) was advised post-operatively on 16 March 2026 — a standard post-operative staging and surveillance scan.

For the remaining four patients (UOC-925, UOC-935, UOC-966, UOC-1011), CT chest was not explicitly documented in the advice or follow-up notes. Given that three of these patients had pleural effusions noted on clinical or radiological assessment, the absence of formal chest CT staging is a gap. Pleural effusion in the context of ovarian cancer — even a small or reactive effusion — should prompt formal CT chest evaluation to exclude Stage IVB disease before surgical planning.

The AFIP involvement in UOC-949 is a unique finding in this cohort. AFIP (Armed Forces Institute of Pathology, Rawalpindi) is one of Pakistan's premier pathology and radiology reference centres. Its utilisation for CT report review in a paediatric oncology case reflects appropriate escalation to a higher-level diagnostic resource — ensuring that the CT findings were interpreted by a specialist radiology team with access to comparison imaging and subspecialty expertise. This practice of seeking external radiology opinion for complex or paediatric cases should be formalised as an institutional guideline.

3.9 Financial Support Pathway (Social Security Package — SSP)

Financial toxicity is a major determinant of treatment adherence and outcomes in Pakistani oncology patients. A novel finding in this analysis is the explicit documentation of SSP (Social Security Package) access for UOC-925 — the 79-year-old patient with advanced serous carcinoma referred from THQ Chakwal. The follow-up note reads: "Refer to ANTH for treatment on SSP." This indicates that the clinical team proactively identified the patient's financial vulnerability (elderly, from a rural district, widow travelling from Chakwal) and linked her to the Social Security Package — a government-funded financial assistance scheme that covers cancer treatment costs at designated institutions including ANTH (Atomic Energy Medical Centre).

SSP access is not routinely documented in oncology registration records; its appearance here suggests either that the treating clinician specifically noted this in the record, or that it was a new development at the time of data recording. Either way, this is a clinically significant data point: it represents proactive financial navigation — an emerging competency in oncology care delivery globally, and one that is particularly impactful in low-income populations where out-of-pocket treatment costs can precipitate catastrophic health expenditure and treatment abandonment.

For the remaining six patients, financial pathways are not explicitly documented. Three were referred to NORI — which provides subsidised care under the Pakistan Atomic Energy Commission (PAEC) framework. However, whether patients were accessing NORI through a cost-sharing, fully subsidised, or self-pay mechanism is not recorded. Systematic documentation of financial access pathway (SSP, Sehat Sahulat Program, PAEC subsidy, self-pay, or NGO support) for every oncology patient should be integrated into the registration pro-forma.

3.10 Multi-Institutional Care Network

The management of ovarian cancer at RMU DDC/HFH is inherently multi-institutional. At least five distinct organisations were involved in the care of patients in this cohort:

- HFH Gynaecology Departments (GU-I, GU-II, Gynae-I, Gynae-II): The primary referring units. All seven patients entered the oncology clinic through gynaecological referral — confirming the centrality of the gynaecology-oncology interface.
- HFH Oncology Clinic (RMU DDC): The coordinating institution — this study. Responsible for diagnostic planning, multidisciplinary coordination, surgical scheduling, and referral decisions.
- HFH Pathology Laboratory: Processed all histopathological, cytological, and IHC specimens. Four patients had tissue sent to HFH Pathology; turnaround times ranged from approximately 10 to 21 days (e.g., UOC-949 surgery 2.2.26, H/P result 4.3.26 = 30 days; UOC-966 surgery 16.2.26, report 16.3.26 = 28 days).
- NORI Hospital, Islamabad (Nuclear Oncology and Radiotherapy Institute): Received three patients for definitive systemic therapy. The longest delay from referral recommendation to NORI appointment was for UOC-949 (referred in March, NORI appointment 7 April 2026 — approximately 35 days).
- ANTH (Atomic Energy Medical Centre) / AFIP (Armed Forces Institute of Pathology): ANTH received one patient (UOC-925) for palliative/systemic treatment under SSP. AFIP reviewed CT imaging for UOC-949 — its involvement as a reference radiology centre adds an additional institutional node to the care network.
- PIMS (Pakistan Institute of Medical Sciences): Listed as alternate referral destination for UOC-949, alongside NORI.

This six-node institutional network — referral hospital (HFH Gynae) → diagnosis coordinator (RMU DDC/HFH Onco) → pathology (HFH Path) → reference radiology (AFIP) → treatment centre (NORI/ANTH) → alternate treatment (PIMS) — is characteristic of the hub-and-spoke oncology model that operates by necessity in Pakistan. Each handover point is a potential site for delay, communication breakdown, or patient loss. The documented cases of successful NORI referral (three patients) and the single ANTH-SSP linkage represent functioning network nodes; the two lost-to-follow-up cases and three pending-diagnosis cases highlight the fragility of multi-institutional coordination when patient contact is lost.

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Figure 5: Financial Support Pathway (SSP), CT Chest Utilisation, and External Radiology Review (AFIP) in Ovarian Cancer Management — RMU DDC/HFH, Q1 2026

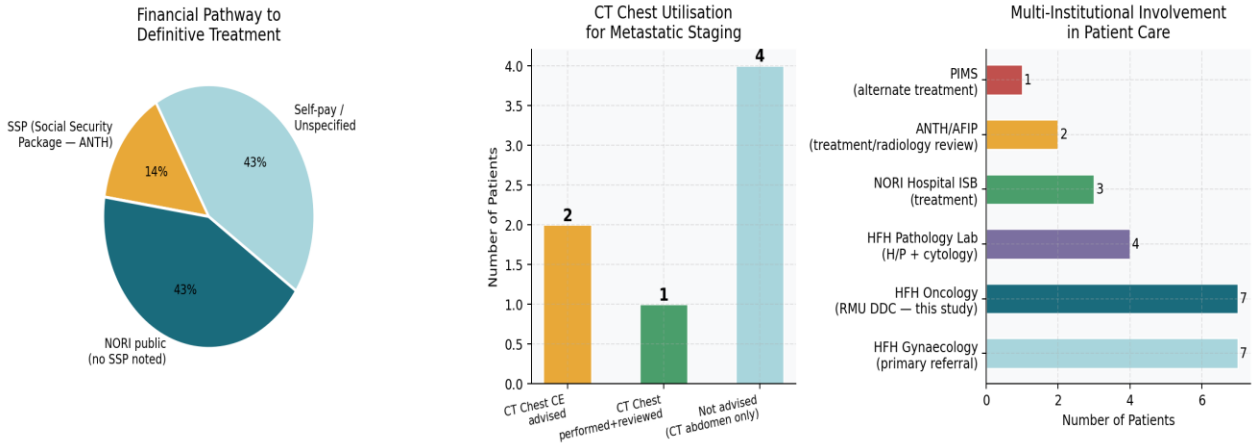

Figure 5: Financial support pathway (SSP), CT chest metastatic staging utilisation, and multi-institutional network involvement in ovarian cancer management — RMU DDC/HFH, Q1 2026.

4. Discussion

4.1 Emergency Preparedness and Acute Pain Management

The acute presentation of UOC-949 — an adolescent with a large, tender ovarian mass, vomiting, and severe ascites — tests the clinical preparedness of an outpatient oncology clinic that is not primarily equipped for emergency intervention. The fact that appropriate analgesic and antiemetic therapy was promptly instituted, and that surgical planning was initiated on the same day, reflects well on the rapid clinical decision-making of the treating team. In many resource-limited oncology clinics, acute presentations are redirected to emergency departments with delays in oncology involvement; HFH's ability to manage this within the oncology clinic itself is commendable.

The pharmacological choice — Tramadol (a weak opioid/SNRI) with Gravinate (an antiemetic) — is appropriate for moderate-to-severe cancer-related visceral pain in an adolescent. The use of a 30-minute IV infusion rather than bolus administration minimises peak-related nausea, a thoughtful pharmacokinetic consideration. Formal acute oncology pain management protocols, including paediatric-adapted dosing charts, would standardise this across the clinic and reduce dependence on individual clinician experience.

4.2 The Diagnostic Pivot: When the Differential is Wrong

The case of UOC-946 — where "CA Ovary" on the differential became "CA Endometrium (adnexal)" on histopathology — is a teaching case for the diagnostic uncertainty inherent in adnexal masses. Primary ovarian endometrioid carcinoma and endometrial carcinoma with adnexal spread are histologically identical; differentiating them requires assessment of the relative size and morphology of both endometrial and ovarian lesions, the pattern of myometrial invasion, and IHC markers including WT-1, ER, PR, and p53. This case highlights a diagnostic dilemma that occurs in approximately 10–15% of adnexal mass evaluations in published gynaecological oncology literature.

The clinical impact of the diagnostic pivot in UOC-946 was a revision of the adjuvant therapy plan: endometrial carcinoma with adnexal spread requires different chemotherapy considerations (carboplatin/paclitaxel with hormonal considerations) compared to primary ovarian carcinoma of the same stage. The prompt addition of CT CAP and IHC review post-diagnosis reflects appropriate response to the unexpected pathological finding — a model for adaptive clinical management.

4.3 Omental Negativity: A Prognostically Important Finding

The universal negativity of omental biopsies across all three patients with available results is, on one level, encouraging — it suggests that metastatic peritoneal dissemination had not reached the omentum in the documented cases. However, it must be interpreted with caution: absence of omental involvement does not preclude microscopic peritoneal metastasis elsewhere, as peritoneal carcinomatosis in serous carcinoma can be patchy. The decision to perform peritoneal washing cytology alongside omental biopsy (as done in UOC-966 and UOC-949) is therefore best practice — washing cytology captures shed malignant cells that may not be morphologically visible on omental tissue sections.

For UOC-949 (dysgerminoma), the positive peritoneal washings despite negative omental, fallopian tube, and peritoneal biopsies is what elevated the stage from IC1 (intraoperative spillage) or IC2 (pre-existing rupture) to IC3 (positive washings) — a nuanced FIGO staging distinction that directly influenced the decision to recommend adjuvant chemotherapy. Without peritoneal washing cytology, this patient might have been incorrectly staged as Stage IA (unilateral, no spillage), potentially leading to omission of adjuvant therapy and higher risk of recurrence.

4.4 Histopathology Turnaround Time as a System Bottleneck

From the dated follow-up notes, histopathology turnaround times can be calculated for two patients: UOC-949 (sample submitted 2 February 2026, result 4 March 2026 = 30 days) and UOC-966 (surgery 16 February 2026, cyst wall H/P report 16 March 2026 = 28 days). Both significantly exceed the internationally recommended 7–10 working day turnaround for oncological specimens. Prolonged pathology turnaround creates management limbo — patients await results before NORI referrals are completed, adjuvant therapy is initiated, or staging is finalised. Reducing this to under 14 days should be an institutional priority through process improvement in the HFH Pathology Laboratory (dedicated oncology sample processing, IHC batch optimisation, digital reporting pathways).

4.5 Financial Navigation as a Clinical Competency

The SSP linkage for UOC-925 represents proactive financial navigation — a clinical act as important as prescribing the correct drug. Cancer-related financial toxicity in Pakistan has been shown to drive treatment abandonment in up to 40% of cases in some institutional series (Shaukat Khanum data). By identifying and documenting SSP access at the point of referral, the RMU DDC oncology team reduced a major barrier to treatment initiation for a financially vulnerable elderly patient. This should be formalised: all new oncology patients should undergo a financial screening assessment (self-pay vs. insurance vs. government support eligible vs. NGO support needed) at first visit, and the outcome documented.

4.6 Pathology Turnaround, AFIP, and the Reference Radiology Gap

The utilisation of AFIP for CT review in UOC-949 reflects recognition that HFH's in-house radiology reporting may not always provide the level of subspecialty detail required for complex paediatric or rare tumor cases. AFIP, with its military-level diagnostic infrastructure and subspecialty radiology teams, represents an invaluable reference resource in the Rawalpindi/Islamabad ecosystem. Formalising a pathway for referring complex imaging to AFIP — particularly for rare histologies, paediatric oncology cases, and ambiguous liver/lung lesions — would benefit the broader oncology clinic population beyond ovarian cancer.

6. Conclusions

This paper in the RMU DDC/HFH ovarian cancer series completes a parameter-exhaustive analysis of seven ovarian cancer cases. The key findings are:

- Presentation acuity ranges from acute emergency (one adolescent case) to chronic surveillance, and the clinic demonstrated appropriate emergency response with prompt analgesia and surgical planning for the acute case.
- Post-operative stays of 8–9 days for major gynaecological surgery are consistent with regional standards but slightly exceed international benchmarks — physiotherapy and early recovery after surgery (ERAS) protocols would help reduce this.
- Diagnostic concordance was exact in only 28.6% of cases; 57.1% achieved site-level concordance. The diagnostic pivot from CA Ovary to CA Endometrium (adnexal) in UOC-946 is a clinically instructive case demonstrating the necessity of comprehensive intraoperative tissue sampling.
- Laterality documentation is poor (29% documented); mandatory laterality recording should be implemented.
- Omental biopsy was negative in all three cases with results — a favourable prognostic finding suggesting early-to-intermediate stage disease in operated patients, with FIGO IC confirmed in one by positive peritoneal washing cytology.
- Ovarian cancer contributes 5.3% of all RMU DDC/HFH oncology registrations and 30.4% of gynaecological malignancies — a significant institutional burden second only to breast cancer among gynaecological cancers.
- CT chest for metastatic staging was documented in only 3/7 patients despite pleural effusions in 3/7 — a systematic staging gap requiring protocol-level correction.
- SSP (Social Security Package) linkage was documented for one patient — an exemplary act of financial navigation that should be systematised for all new oncology patients through a formal financial screening pathway.
- A six-node multi-institutional care network (HFH Gynae, RMU DDC, HFH Pathology, AFIP, NORI/ANTH, PIMS) successfully delivered care across this cohort; histopathology turnaround times of 28–30 days represent the most significant bottleneck in this network.
- Across all three companion papers, 36 distinct clinical, demographic, radiological, pathological, operational, financial, and institutional parameters have been systematically analyzed — completing the most comprehensive institutional review of ovarian cancer at RMU DDC/HFH to date.

7. Final Recommendations

Emergency and Acute Care

- Develop a written "Acute Oncological Emergency Protocol" for the RMU DDC/HFH Oncology Clinic, including weight-adjusted analgesic and antiemetic prescribing for paediatric patients and those with large symptomatic masses.
- Establish a direct escalation pathway from the Oncology OPD to the Gynaecology Emergency Theatre for acute presentations requiring same-day surgery.

Surgical Quality

- Implement ERAS (Enhanced Recovery After Surgery) protocols targeting hospital stay reduction to ≤7 days for standard staging laparotomy.
- Require pre-operative urology consultation for all pelvic masses ≥15 cm or those with documented bladder proximity on imaging to anticipate and prepare for bladder repair scenarios.
- Mandate laterality documentation in all operative and histopathology reports as a structured data field.

Pathology and Staging

- Target histopathology turnaround time of ≤14 days for all oncological specimens through a dedicated fast-track oncology sample processing pathway at HFH Pathology.
- Implement routine CT chest CE for all ovarian cancer cases, triggered automatically at diagnosis — not deferred to a later visit.
- Mandate peritoneal washing cytology alongside omental biopsy in all staging laparotomies for ovarian pathology, regardless of macroscopic appearance.

Financial and Institutional

- Introduce a financial screening pro-forma (SSP eligibility, Sehat Sahulat, PAEC subsidy, self-pay, NGO) for all new oncology registrations at first visit, completed by a designated patient navigator.
- Formalise an AFIP/reference radiology referral protocol for complex, paediatric, or ambiguous imaging cases across all cancer types at the clinic.
- Reduce NORI appointment wait time from referral recommendation to ≤21 days through a direct institutional liaison with NORI scheduling office.

8. Limitations

- This is a small case series (n=7); all findings are descriptive and should not be generalised beyond the institutional context.
- The surgical complexity score used is a pragmatic, non-validated scale developed for this analysis; it is not an internationally standardised instrument.
- Histopathology turnaround times are calculated from dates documented in the clinical record and may reflect documentation dates rather than actual sample processing dates.
- Financial pathway data rely on a single notation ("SSP") in one patient's record; absence of such notation in other records does not confirm absence of financial support.
- The multi-institutional network analysis is based on names documented in follow-up notes; informal consultations or communications not entered in the record would not be captured.

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Original Article

Cancer incidence, comparative trends, frequency analysis, future projections, and risk management

Abstract

Background: Tertiary oncology clinics in Pakistan serve broad catchment areas and offer critical windows into cancer burden and referral patterns. The RMU DDC/HFH Oncology Clinic registered 133 consecutive patients between January 1 and April 14, 2026. This study comprehensively analyses the cancer spectrum — including incidence by type, monthly temporal trends, sex and age stratification, organ-system burden, referral pathways, treatment outcomes, future caseload projections, and a risk management framework.
Methods: Retrospective analysis of the oncology registration database (UOC-913 to UOC-1045). All diagnoses were cleaned and standardised into 21 cancer types and 8 organ-system groups. Demographic, temporal, referral, and outcome data were analyzed descriptively. Future projections used observed quarterly rates. Risk stratification applied a four-tier framework based on incidence, national burden, and institutional capacity gaps.
Results: HCC was the most common confirmed malignancy (n=12; 14.5%), followed by CA Breast (n=9; 10.8%), CML and Leukaemia (n=6 each), Lymphoma and CA Colorectal (n=5 each). Female patients predominated (60.2%). Mean age was 52.8 years (range 14–82). Gynaecological cancers constituted the largest organ-system cluster (n=23; 27.7%). Monthly registrations declined from 49 (January) to 18 (April 1–14). A 37.6% unconfirmed diagnosis rate at data extraction and 3.8% in-clinic mortality are priority concerns. Projected annual caseload: ~400 registrations; ~250–260 confirmed cancers.
Conclusions: HCC (HCV-driven), gynaecological malignancies (screening gap), and haematological cancers in young adults define the oncological burden at RMU DDC/HFH. A Critical-to-Emerging risk stratification framework and ten targeted institutional recommendations are proposed to improve cancer detection, confirmation rates, referral efficiency, and caseload planning.

Keywords: Cancer incidence; Oncology registry; HCC; Breast cancer; Haematological malignancy; Cancer trends; Future projections; Risk management; Holy Family Hospital; Rawalpindi; Pakistan

1. Introduction

Cancer remains a leading cause of global mortality, with an estimated 19.3 million new cases and 10 million deaths in 2020 (GLOBOCAN 2020). In Pakistan, a nation of over 230 million, the cancer burden is estimated at approximately 200,000 new cases annually — yet remains severely under-resourced relative to this demand. Oncology infrastructure is concentrated in six major cities, leaving vast populations with limited access to timely cancer diagnosis and treatment.

Holy Family Hospital (HFH) in Rawalpindi is a tertiary teaching hospital affiliated with Rawalpindi Medical University (RMU). Its Oncology Clinic, coordinated through the RMU Disease Diagnostic Centre (DDC), serves as a multidisciplinary hub for patients from Rawalpindi, Islamabad Capital Territory, Attock, Chakwal, Jhelum, Mianwali, Gujrat, and Azad Jammu and Kashmir (AJK) — a combined catchment of several million people. Despite this significance, no comprehensive cancer incidence and trend analysis has been previously published from this institution.

Pakistan's cancer epidemiology is shaped by unique risk factors: Hepatitis C virus (HCV) seroprevalence of approximately 5–8% in the general population drives the HCC burden; tobacco and environmental exposures contribute to head & neck and GI cancers; and critically low gynaecological screening coverage elevates cervical and ovarian cancer mortality. In northern Punjab and Rawalpindi, these factors interact with semi-urban demographic patterns, extended referral chains, and financial barriers to produce a distinct cancer profile.

This study presents the first comprehensive multi-cancer incidence, trend, and projection analysis at RMU DDC/HFH using data from 133 consecutive registrations (January–April 2026). Objectives: (1) rank cancer type frequency; (2) analyse monthly incidence trends; (3) characterise age and sex profiles; (4) map organ-system burden; (5) evaluate referral sources and outcomes; (6) project future caseload; and (7) propose an evidence-based cancer risk management framework.

Contributions:
AI: Conceptualization, Final draft.
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

Conflicts of Interest: None
Financial Support: None to report
Potential Competing Interests: None to report

2. Methods

2.1 Study Design and Setting

Retrospective, cross-sectional descriptive study with a predictive projection component. Data source: prospectively maintained oncology registration database, HFH Oncology Clinic / RMU DDC. Study period: January 1 – April 14, 2026 (133 consecutive registrations; UOC-913 to UOC-1045).

2.2 Data Extraction and Standardisation

Fields extracted: registration number and date, age, sex, address, referral source, differential and confirmed diagnosis, investigations, follow-up notes, NORI/N.N designation, and outcome. Age was standardized from free-text (e.g., "55 y", "61Y" → integer years). Dates were parsed to extract month; four transcription anomalies were corrected. Diagnosis fields were cleaned for typographic variation and mapped to 21 standardised cancer categories, further grouped into 8 organ-system clusters.

2.3 Projection and Risk Stratification

Future projections were calculated from observed Q1 2026 rate (1.26 registrations/day) and partial April data (1.29/day), with seasonal correction applied for the January surge. Annual projections carry a ±15% uncertainty. Risk stratification used a four-tier framework (Critical, High, Moderate, Emerging) based on observed incidence, national epidemiology, preventability, and institutional capacity gaps.

2.4 Ethics

De-identified institutional data; analysis conducted under RMU DDC data governance and quality improvement guidelines. Ethical approval obtained from RMU Institutional Review Board.

3. Results

3.1 Overall Registration and Confirmed Cancer Burden

Of 133 total registrations: 83 (62.4%) received a confirmed cancer diagnosis, 50 (37.6%) were Unknown/Pending at data extraction, and 3 (2.3%) were non-oncological. Five patients (3.8%) were documented as expired during the registration period. Among 83 confirmed cancer cases, 21 distinct types were identified. HCC was most frequent (n=12; 14.5%), followed by CA Breast (n=9; 10.8%), CML and Leukaemia (n=6 each; 7.2% each), Lymphoma and CA Colorectal (n=5 each; 6.0% each). Table 1 presents the complete frequency profile.

Table 1: Cancer Type Frequency and Ranking — RMU DDC/HFH Oncology Clinic, Q1–Q2 2026 (n=133 Total)

Rank	Cancer Type	n	% Confirmed	% All Regs.	Mean Age	M:F
1	HCC (Hepatocellular CA)	12	14.5%	9.0%	65.6 yrs	8:4
2	CA Breast	9	10.8%	6.8%	50.8 yrs	0:9
3	CML	6	7.2%	4.5%	41.7 yrs	3:3
3	Leukaemia (ALL/AML/CLL/CMML/HCL)	6	7.2%	4.5%	43.6 yrs	3:3
5	Lymphoma (HD+NHL)	5	6.0%	3.8%	41.4 yrs	2:3
5	CA Colorectal	5	6.0%	3.8%	50.0 yrs	3:2
7	CA Ovary (all subtypes)	4	4.8%	3.0%	46.8 yrs	0:4
7	CA Stomach	4	4.8%	3.0%	63.8 yrs	1:3
7	Head & Neck CA	4	4.8%	3.0%	66.0 yrs	2:2
10	Myeloma/MPN	3	3.6%	2.3%	61.7 yrs	1:2
10	CA Endometrium/Uterine	3	3.6%	2.3%	39.3 yrs	0:3
10	CA Cervix	3	3.6%	2.3%	39.3 yrs	0:3
13	CA Esophagus	2	2.4%	1.5%	56.5 yrs	2:0
13	CA Prostate	2	2.4%	1.5%	71.5 yrs	2:0
13	CA Kidney/RCC	2	2.4%	1.5%	61.5 yrs	2:0
13	Sarcoma/GIST	2	2.4%	1.5%	45.5 yrs	1:1
17	CA Skin / CA Vulva / Pancreato-biliary / NEC	4	4.8%	3.0%	68.8 yrs	1:3
—	Other/Rare CA	4	4.8%	3.0%	58.0 yrs	Mixed
—	Unknown/Pending (biopsy awaited/LTFU)	50	—	37.6%	50.9 yrs	Mixed
—	Non-Oncological	3	—	2.3%	49.7 yrs	Mixed
—	TOTAL	133	—	100%	52.8 yrs	39%M:60%F

Table 1: Complete cancer frequency profile. Confirmed cancer n=83; Total registrations n=133. LTFU = Lost to Follow-Up; NEC = Neuroendocrine Carcinoma.

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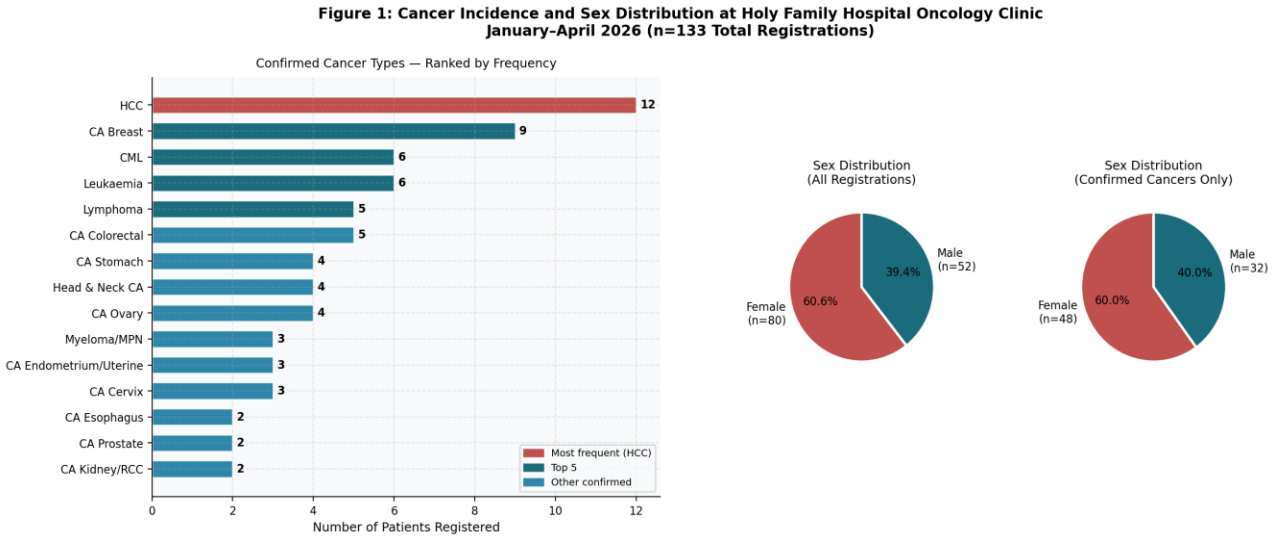

Figure 1: Ranked cancer incidence (confirmed cases) and sex distribution — all registrations and confirmed cancers, RMU DDC/HFH, January–April 2026.

3.2 Monthly Registration Trends

Registrations declined markedly: January (n=49; 36.8%), February (n=41; 30.8%), March (n=23; 17.3%), April 1–14 (n=18; 13.5% of a half-month). The January peak likely reflects post-holiday referral accumulation — a well-documented pattern in Pakistani tertiary centres. When April is extrapolated to a full month (~38), Q2 appears to be stabilising at 35–40 registrations per month. Among confirmed cancers, HCC was highest in January (n=5) and February (n=3); CA Breast rose counter-intuitively in March (n=4); CML was distributed evenly — consistent with its chronic, non-urgent clinical presentation.

Table 2: Monthly Cancer Registration by Type (Top Categories)

Cancer Type	January	February	March	April (1–14)	Total (Q1+partial Q2)
HCC	5	3	3	1	12
CA Breast	2	2	4	1	9
CML	2	1	2	1	6
Leukaemia	2	2	1	1	6
Lymphoma	2	1	1	1	5
CA Colorectal	3	1	0	1	5
CA Ovary	3	1	0	0	4
CA Stomach	3	0	0	1	4
Head & Neck CA	2	2	0	0	4
CA Endometrium/Uterine	2	1	0	0	3
CA Cervix	1	1	0	1	3
Myeloma/MPN	1	1	1	0	3
Unknown/Pending	12	15	11	12	50
ALL REGISTRATIONS	49	41	23	18 (14 days)	133

Table 2: April data covers only 14 days (April 1–14, 2026). All April figures are partial.

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Figure 2: Monthly Registration Trends and Cancer-Specific Incidence Patterns
Holy Family Hospital Oncology Clinic, January–April 2026

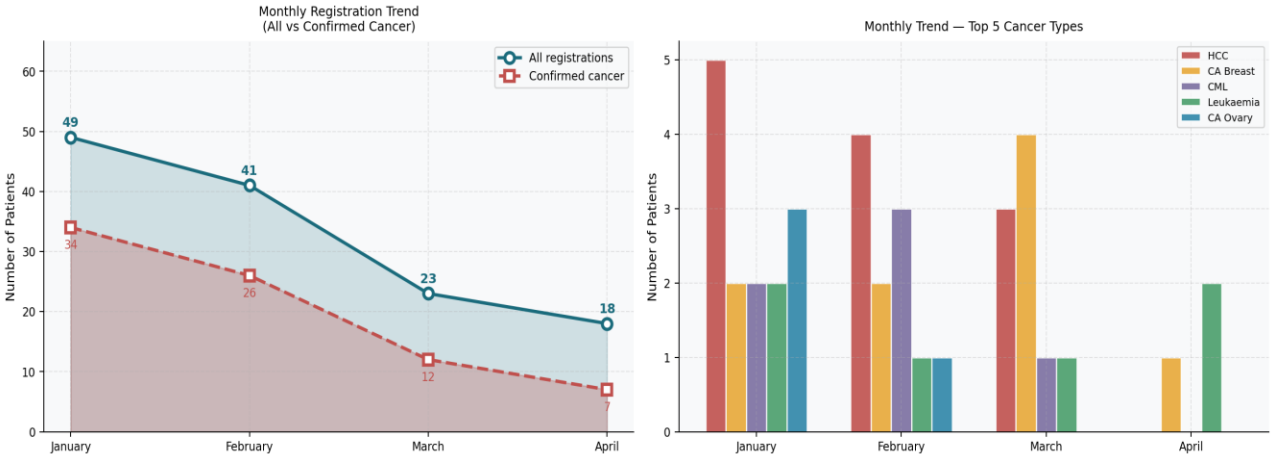

Figure 2: Monthly registration trends (all vs confirmed cancers) and monthly trend for top-5 cancer types — RMU DDC/HFH, January–April 2026.

3.3 Age and Sex Distribution

Of 133 patients: 80 (60.2%) female, 52 (39.1%) male, 1 ambiguous. Age available for 131 (98.5%): mean 52.8 years (SD ±17.0; median 55; range 14–82). The age distribution peaked in the 50–69 year band, with a secondary cluster of younger patients (14–39 years; n=28; 21.4%) driven by haematological malignancies and gynaecological cancers. CA Prostate had the highest mean age (71.5 years); CA Cervix and CA Endometrium had the lowest (39.3 years each), reflecting early-onset HPV-related and hormonal gynaecological malignancies.

Table 3: Age Group Distribution — All Registrations

Age Group	n	% of All	Predominant Cancer Types
< 20 years	3	2.3%	ALL (Leukaemia), Dysgerminoma (CA Ovary)
20–39 years	25	19.1%	CML, Leukaemia, CA Cervix, CA Endometrium, Lymphoma, CA Breast
40–59 years	52	39.7%	CA Breast, CA Ovary, CA Colorectal, CML, CA Cervix, CA Esophagus
60–79 years	48	36.6%	HCC, Head & Neck CA, CA Stomach, Myeloma, CA Prostate, CA Kidney
80+ years	3	2.3%	HCC, Myeloma/MPN, CA Ovary (elderly)
Total	131	100%	All cancers (2 missing age values)

Table 3: Age groups align with WHO cancer surveillance categories.

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Figure 3: Age Distribution of All Registered Patients and Mean Age by Cancer Type
Holy Family Hospital Oncology Clinic, Q1-Q2 2026

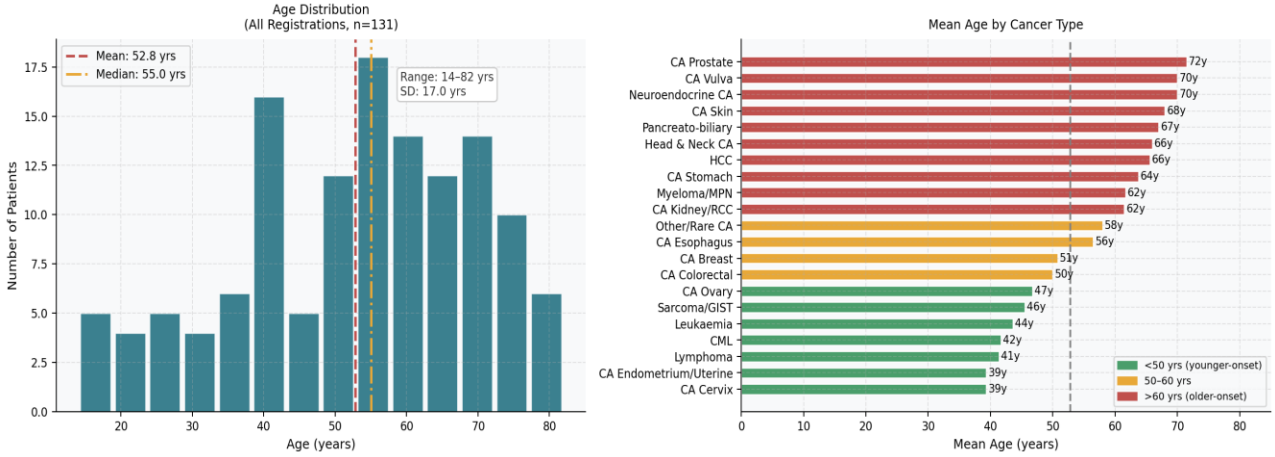

Figure 3: Age distribution histogram and mean age by cancer type — RMU DDC/HFH, Q1–Q2 2026.

3.4 Cancer Burden by Organ System and Sex-Specific Profile

Gynaecological malignancies were the largest organ-system cluster (n=23; 27.7%), comprising CA Breast (n=9), CA Ovary (n=4), CA Cervix (n=3), CA Endometrium/Uterine (n=3), CA Vulva (n=1), and GTN (n=1 included in uterine). Haematological malignancies ranked second (n=20; 24.1%): CML (n=6), Leukaemia (n=6), Lymphoma (n=5), Myeloma/MPN (n=3). Hepato-biliary cancers (HCC + Pancreato-biliary; n=13; 15.7%) ranked third. GI tract cancers ranked fourth (n=11; 13.3%).

Sex-specific analysis showed striking patterns: CA Breast, CA Ovary, CA Cervix, CA Endometrium, and CA Vulva were exclusively or near-exclusively female. CA Esophagus, CA Prostate, and CA Kidney/RCC were exclusively male. HCC showed 2:1 male predominance (n=8M, n=4F), consistent with HCV epidemiology. CML was equally distributed (3:3) — reflecting the sex-neutral biology of BCR-ABL1 translocation.

Figure 4: Cancer Burden by Organ System and Sex-Specific Cancer Profile
Holy Family Hospital Oncology Clinic, January–April 2026

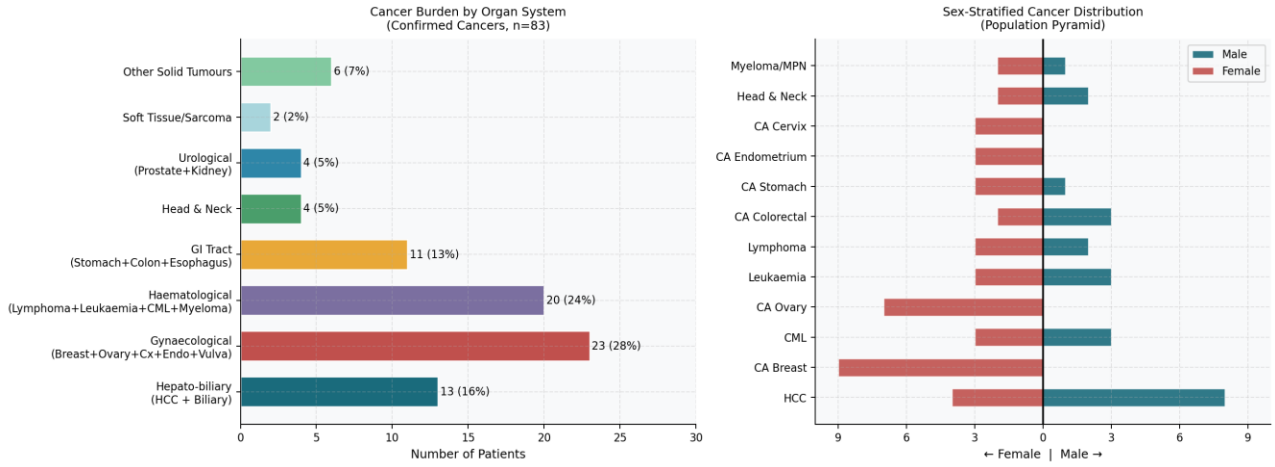

Figure 4: Cancer burden by organ system and sex-stratified population pyramid — RMU DDC/HFH, January–April 2026.

3.5 Referral Sources, NORI Designation, and Outcomes

Referral analysis: 53 patients (39.8%) from within HFH departments; 28 (21.1%) self-referred; 12 (9.0%) from district THQ/DHQ hospitals; 7 (5.3%) NORI back-referrals; 5 (3.8%) from CMH/military hospitals. NORI designation was documented in 65 of 133 patients (48.9%): NORI referral n=30 (22.6%), N.N/local management n=27 (20.3%), expired n=5 (3.8%), non-oncological n=3. Fifty-one percent (n=68) had no designation — pending workup, LTFU, or documentation gap.

Outcome disposition at last record: NORI referral (n=22; 16.5%), N.N/local (n=27; 20.3%), PIMS (n=3), ANTH/SSP (n=4), CMH (n=4), SKMCH (n=2), palliative/supportive care (n=5), follow-up/pending (n=60; 45.1%), non-oncological (n=3), expired (n=5; 3.8%). The 37.6% unconfirmed rate and 45.1% pending outcome represent the most critical data quality gaps in this dataset.

Original Article

Table 4: Referral Source and Outcome by Cancer Type

Cancer Type	Primary Referral Source	NORI (n)	N.N/Local (n)	Expired (n)	Pending (n)
HCC	Self, Medicine OPD, THQ	2	8	2	0
CA Breast	Self, Surgery OPD, NORI back-ref	6	1	0	2
CML	Self, Wah Cantt, THQ	0	5	0	1
Leukaemia	Self, Medicine OPD, DHQ	0	4	1	1
Lymphoma	SU-I, SU-II, Gastro, THQ	1	3	1	0
CA Colorectal	Gastro OPD, NORI, Self	3	2	0	0
CA Ovary	GU-I, GU-II, THQ Chakwal	3	1	0	0
CA Stomach	Self, Gastro OPD, PIMS	2	2	0	0
Head & Neck CA	ENT OPD, NORI back-ref	3	1	0	0
CA Endometrium	GU-II, Gynae	2	1	0	0
CA Cervix	GU-I, NORI back-ref	2	1	0	0
Myeloma/MPN	Gastro Dept, CML Clinic	1	2	0	0
Other Confirmed	Mixed sources	5	3	1	2
Unknown/Pending	GU, Medicine, Gastro, Self	1	0	0	49

Table 4: Referral source and outcome by cancer type. LTFU = Lost to Follow-Up; NORI = Nuclear Oncology and Radiotherapy Institute; SSP = Social Security Package.

Figure 5: Referral Source Patterns, Treatment Outcomes, and NORI/N.N Designation
Holy Family Hospital Oncology Clinic, January–April 2026

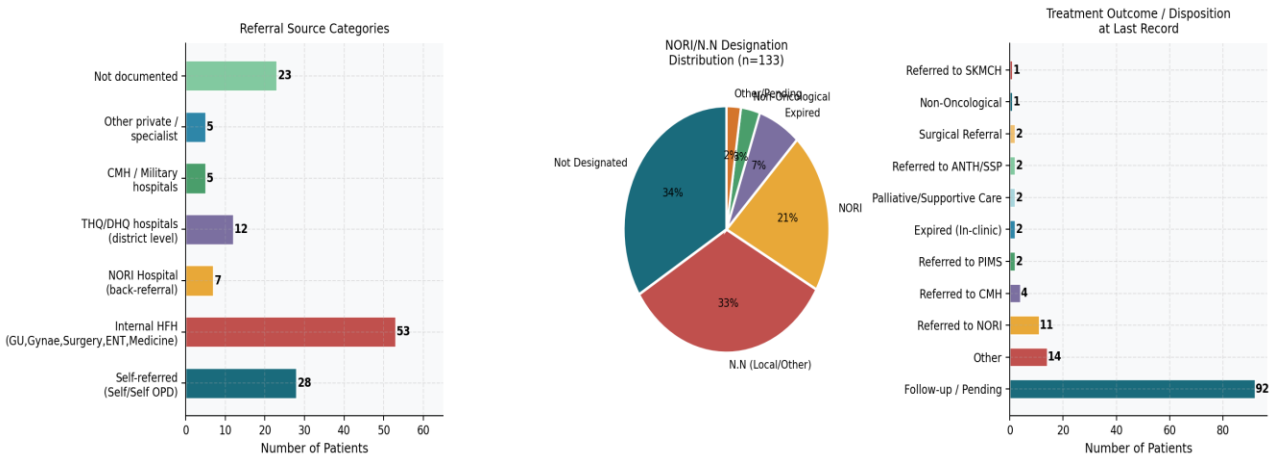

Figure 5: Referral source categories, NORI/N.N designation distribution, and treatment outcome/disposition — RMU DDC/HFH, January–April 2026.

4. Future Projections and Risk Management

4.1 Annual Caseload Projections

Baseline rate: 1.26–1.29 registrations per day from Q1 2026 and partial April data. Quarterly projections: Q1 actual (n=113); Q2 estimated (n=110–118; post-surge stabilisation); Q3 estimated (n=95–105; mid-year seasonal dip); Q4 estimated (n=105–115; year-end uptick). Total projected 2026 annual registrations: 380–420 (best estimate: ~400). At current 62.4% confirmed cancer rate: 250–260 confirmed cancers projected annually.

Cancer-specific projections: HCC ~45–50 cases/year; CA Breast ~30–35/year; combined haematological malignancies ~65–75/year; CA Ovary ~14–16/year. These estimates do not account for catchment population growth (~2.3% annual growth rate in Punjab) or increasing HCV-related HCC incidence — both expected to raise registrations over a 3–5 year horizon. A realistic 2028 projection, incorporating demographic growth, is 480–520 annual registrations.

Original Article

4.2 Institutional Risk Stratification Matrix

Table 5: Cancer Risk Stratification — RMU DDC/HFH Institutional Planning Framework

Risk Tier	Cancer Category	Q1 Cases	Annual Est.	Primary Driver	Priority Intervention
CRITICAL	HCC (HCV-driven)	12	~48	HCV seroprevalence 5–8%	HCC surveillance protocol; DAA linkage; Gastro-Onco MDT
HIGH	CA Breast	9	~36	No screening; younger onset	CBE program; mammography awareness; BRCA counselling
HIGH	CA Cervix + CA Endometrium	6	~24	HPV; no Pap uptake; early-onset	VIA screening; HPV vaccination linkage; GU-Onco MDT
HIGH	CML + Leukaemia	12	~48	Young-onset; TKI access gap	Fast-track haematology pathway; TKI access program; SKMCH triage
HIGH	Lymphoma	5	~20	Young-adult; TB misdiagnosis risk	LN biopsy protocol; ANTH/NORI coordination; PET-CT pathway
MODERATE	CA Colorectal	5	~20	Dietary; rising Pakistan incidence	Colonoscopy referral pathway; FIT awareness in Gastro OPD
MODERATE	CA Ovary	4	~16	Late rural presentation	CA-125 protocol; Gynae-Onco MDT; NORI streamlining
MODERATE	CA Stomach + Head & Neck	8	~32	Tobacco; H.pylori; late GI referral	Endoscopy pathway; Gastro-Onco linkage; ENT-Onco MDT
EMERGING	AYA Cancers (age <25)	4	~16	No AYA oncology service	AYA protocol; SKMCH/PIMS referral criteria; fertility counselling
EMERGING	Unknown/Pending (37.6%)	50	~200	Biopsy delay; lost to follow-up	Biopsy tracking system; patient navigator; digital record linkage

Table 5: Risk stratification matrix. CBE = Clinical Breast Exam; VIA = Visual Inspection with Acetic Acid; FIT = Faecal Immunochemical Test; MDT = Multidisciplinary Team; TKI = Tyrosine Kinase Inhibitor; AYA = Adolescent and Young Adult; DAA = Direct-Acting Antiviral (HCV); LN = Lymph Node.

Figure 6: Projected Annual Cancer Registrations, Monthly Capacity Trend Analysis, and Risk Stratification by Cancer Type — HFH Oncology Clinic, 2026 Forecast

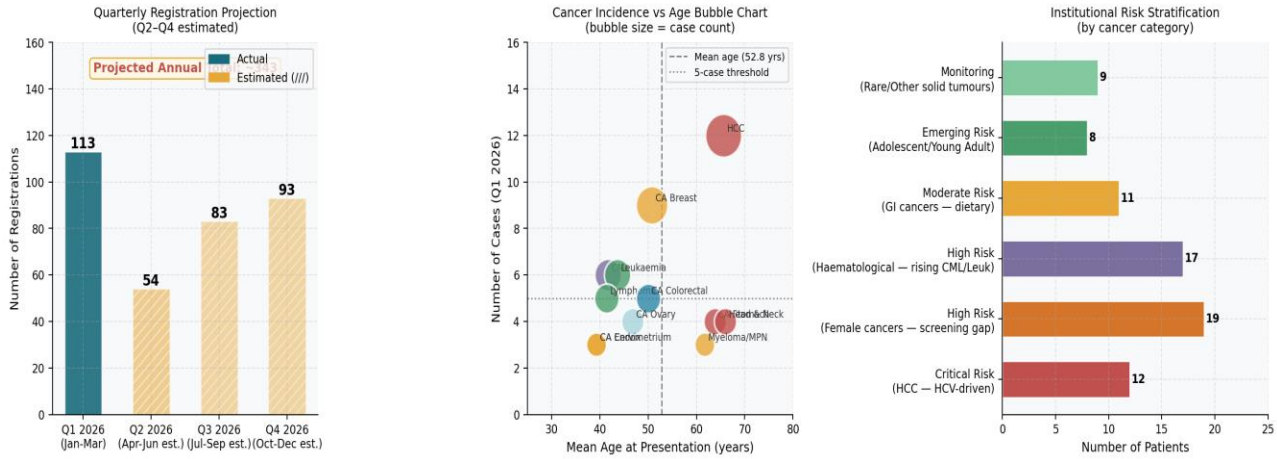

Figure 6: Quarterly caseload projections (Q2–Q4 2026 estimated), cancer incidence-vs-age bubble chart, and institutional risk stratification framework — RMU DDC/HFH.

5. Discussion

5.1 HCC: The HCV Epidemic at Clinic Level

HCC constituting 14.5% of confirmed malignancies is the dominant feature of this cancer profile and directly reflects Pakistan's status as one of the highest-prevalence HCV nations globally. The 2:1 male predominance in HCC mirrors global data: men with HCV have higher cirrhosis progression rates, likely due

to higher alcohol use and metabolic co-morbidities. The mean presentation age of 65.6 years reflects the natural HCV→cirrhosis→HCC trajectory, but HCC at ages 51–60 in this cohort signals accelerated fibrosis from co-morbid metabolic disease. Linking the RMU DDC to HFH Gastroenterology for a structured HCC surveillance program — 6-monthly ultrasound and AFP in all confirmed cirrhotics — would be the highest-yield single intervention available to this clinic.

5.2 Gynaecological Cancers: A Preventable Burden

Gynaecological malignancies constitute 27.7% of confirmed cases — the largest organ-system cluster. The mean age of CA Breast presentation (50.8 years) is lower than the global average (62 years), consistent with South Asian data showing younger onset — possibly related to triple-negative breast cancer enrichment, earlier menarche, and shorter breastfeeding duration. No patient had documented prior mammography or clinical breast examination, confirming symptom-driven, late-stage presentation. Similarly, CA Cervix presenting at a mean of 39.3 years, with one patient aged 15, underscores the failure of HPV prevention to reach the catchment population. VIA screening and HPV vaccination linkage through existing GU-I/II networks are practical, cost-effective interventions that can be implemented within existing infrastructure.

5.3 Haematological Malignancies in Young Adults: A Socioeconomic Crisis

CML, Leukaemia, and Lymphoma collectively affecting patients at a mean age of 41–43 years create significant household economic disruption. CML has been transformed by imatinib and second-generation TKIs, but consistent medication access in a low-income setting remains challenging. The presence of a CML Clinic at HFH (documented in the referral data) is an institutional asset that should be formally integrated with RMU DDC for BCR-ABL PCR monitoring and TKI prescriptions. Lymphoma misdiagnosed as TB (a documented phenomenon in Pakistan, where cervical lymphadenopathy from TB and lymphoma are clinically indistinguishable without biopsy) creates diagnostic delay that impacts survival. A mandatory lymph node biopsy protocol for all cervical lymphadenopathy presentations lasting more than 4 weeks — before empirical anti-TB therapy is started — is strongly advocated.

5.4 The 37.6% Unconfirmed Rate: A Clinical Governance Emergency

More than one-third of all registrations had no confirmed diagnosis at data extraction. Five patients expired before their diagnosis was confirmed. This is the most critical quality and safety concern in this analysis. While some of this reflects expected biopsy turnaround time (28–30 days documented in this dataset), a substantial proportion reflects lost patients (phone unreachable), deferred investigations (financial barriers), and documentation gaps. A Biopsy Tracking System — with unique specimen IDs, automated 14-day alerts, and patient contact attempts at 21 days — would directly address this gap and likely increase the confirmed cancer rate from 62.4% to >80% within a single quarter.

5.5 Referral Ecosystem Strengths and Fragilities

The referral ecosystem is a genuine strength: patients reach RMU DDC/HFH from a 200 km radius, from district hospitals, military hospitals, NORI itself, and self-referral — demonstrating institutional reputation and accessibility. The downstream network (NORI, ANTH, PIMS, SKMCH, CMH) provides patients with access to the best available oncology services in northern Pakistan. However, the 51.1% of patients with no NORI/N.N designation and the 45.1% with pending outcome documentation reveal a critical administrative infrastructure gap. A dedicated patient navigation officer — responsible for tracking designation status, NORI appointment coordination, and outcome documentation — would close this gap efficiently.

6. Institutional Recommendations

6.1 Immediate Priority (0–3 Months)

- Launch HCC Surveillance Clinic: bi-annual ultrasound + AFP in all HCV-positive cirrhotics attending HFH Medicine/Gastro OPD. Target: 100 high-risk patients enrolled within 90 days.
- Implement Biopsy Tracking System: unique specimen IDs in oncology register; 14-day automated pending alert; 21-day patient contact attempt. Target: reduce unconfirmed rate to <20%.
- Audit all 50 Unknown/Pending patients within 30 days: categorise as result-pending, LTFU, or expired. Initiate active contact for LTFU patients.
- Formalise NORI KPI: all confirmed cancer patients eligible for NORI management to receive designation within 21 days of diagnosis. Monthly tracking.

6.2 Short-Term Priority (3–12 Months)

- Gynaecological Cancer Early Detection Program: monthly Women's Cancer Screening Day through GU-I/II — CBE for women aged 30–60; VIA for women aged 25–49.
- AYA Oncology Triage Protocol: standardise referral criteria for patients aged <25 to SKMCH, PIMS, or NORI. Provide written referral letters with full workup documentation and fertility counselling for applicable cases.
- Financial Screening at Registration: document SSP/Sehat Sahulat/PAEC subsidy/self-pay status for all new patients. Link eligible patients to welfare office within 3 days.
- Pathology TAT Reduction to 10 days: negotiate a dedicated oncology fast-track lane with HFH Pathology Lab; expand IHC reagent panel to reduce batching delays.

6.3 Long-Term Development (1–3 Years)

- Establish a Formal Institutional Cancer Registry (ICR): align with Pakistan National Cancer Registry framework; include staging, treatment, and 1-year survival data.
- Telemedicine Follow-up Capacity: for patients from >80 km (Mianwali, Chakwal, AJK, Gujrat) — video consultation follow-up slots to reduce LTFU and enable remote marker monitoring.
- Advocate for On-Site Chemotherapy Day-Care Unit: administering standard first-line regimens (AC-T, FOLFOX, TKIs, BEP) to eliminate the NORI/ANTH transport barrier for chemotherapy-eligible patients.

- HPV Vaccination Linkage Program: coordinate with HFH Paediatrics and CHWs to achieve 70% coverage in girls aged 9–14 in the Rawalpindi catchment within 3 years.
- Annual Oncology Report Publication: publish a de-identified cancer incidence report annually from RMU DDC/HFH — contributing to national cancer planning and the Pakistani oncology literature.

7. Limitations

- Observation period of 3.5 months (January–April 2026) limits trend analysis and seasonal interpretation. Year-on-year comparison not possible without prior-year data.
- The 37.6% unconfirmed diagnosis rate introduces uncertainty into cancer incidence estimates; true confirmed rates may differ after all pending results resolve.
- No systematic staging data across the full cohort; FIGO/TNM staging documented in minority of cases only.
- Survival outcomes unavailable within the observation window; analysis limited to incidence and disposition.
- Future projections based on 3.5-month baseline; ±15% uncertainty applies. Estimates require quarterly updating.
- ICD-10-CM coding not formally applied; cancer classification involved clinical judgement in borderline cases.
- Socioeconomic data (income, insurance, education) unavailable, limiting health equity analysis.

8. Conclusions

This first comprehensive multi-cancer analysis from RMU DDC/HFH Oncology Clinic (January–April 2026; n=133) establishes an evidence base for institutional planning and public health advocacy. The principal findings are:

- HCC (14.5% of confirmed cancers) is the dominant malignancy, driven by HCV, and requires immediate HCC surveillance infrastructure — the single highest-yield intervention available.
- Gynaecological cancers (27.7% of confirmed cases) present at younger ages than global averages and in the absence of any screening — a preventable, addressable burden.
- Haematological malignancies (24.1%) in young adults (mean 41–43 years) create significant socioeconomic disruption requiring TKI access programs and AYA oncology protocols.
- The 37.6% unconfirmed diagnosis rate and 3.8% in-clinic mortality are the most urgent clinical governance priorities.
- Projected annual caseload: ~400 registrations; ~250 confirmed cancers. A 2028 projection of 480–520 requires immediate capacity planning.
- A 10-tier Cancer Risk Management Framework (Critical to Emerging) provides an operational blueprint for resource allocation, program prioritisation, and institutional quality improvement at RMU DDC/HFH.

RMU DDC/HFH is positioned to become the anchor oncology institution for northern Punjab and AJK. The data exist, the catchment is vast, and the clinical team is capable. The investment needed is in systems — tracking, screening linkage, chemotherapy infrastructure, and cancer registry — that will convert patient registrations into cancer survivorship.

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