Factors Associated with Survival Outcomes in Ovarian Cancer Patients in Karachi, Pakistan: Results from a Single-Institution Cancer Registry

Uzma Shamsi[1], Namra Usman[1], Azmeena Tajuddin[2] and Uzma Chishti[3]

[1]*Department of Community Health Sciences, The Aga Khan University, Karachi, Pakistan*
[2]*Department of Oncology, The Aga Khan University, Karachi, Pakistan*
[3]*Department of Obstetrics and Gynaecology, The Aga Khan University, Karachi, Pakistan*

ABSTRACT

Objective: To evaluate survival outcomes and identify sociodemographic and clinicopathological factors associated with survival among women diagnosed with ovarian cancer (OC) in Karachi, Pakistan.

Study Design: Retrospective cohort study.

Place and Duration of the Study: The Aga Khan University Hospital, Karachi, Pakistan, between 2010 and 2020.

Methodology: A total of 966 women aged 18–91 years with OC were identified from the University Hospital cancer registry. Data on vital status and last contact dates were updated. Sociodemographic characteristics, tumour features, stage, CA125 levels, and treatment modalities were analysed. Survival was assessed as the primary endpoint using Kaplan-Meier survival analysis and Cox proportional hazards models, with hazard ratios (HR) and 95% confidence intervals (CI) reported.

Results: Patients who did not undergo cytoreductive surgery exhibited the highest mortality risk (HR: 3.94; CI: 2.69–5.76), followed by those who underwent suboptimal cytoreduction surgery (HR: 2.01; CI: 1.29–3.13) compared to those who underwent optimal cytoreduction surgery. Chemotherapy significantly reduced mortality risk (HR: 0.56; CI: 0.39–0.82). Recurrence was a critical determinant of poor survival, with the highest risk observed in patients who were never disease-free (HR: 10.81; CI: 6.12–19.07) or experienced recurrence (HR: 7.44; CI: 4.31–12.86).

Conclusion: Optimal cytoreduction surgery and chemotherapy are essential in improving survival outcomes for OC patients. Recurrence remains a significant determinant of poor prognosis. Enhancing early detection, optimising treatment strategies, and strengthening healthcare infrastructure are critical for improving survival outcomes among OC patients in Karachi.

Key Words: *Ovarian cancer, Survival outcomes, Cytoreductive surgery, Chemotherapy, Recurrence*.

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INTRODUCTION

Ovarian cancer (OC) is a heterogeneous disease with a low incidence but poor prognosis, typically discovered in its advanced stages.[1] OC is the eighth most common cancer in women worldwide, with an increasing incidence rate in Eastern Europe and Asia.[2] According to Karachi Cancer Registry (KCR), OC is the second most common malignancy in women in Karachi, Pakistan.[3]

Ovarian cancer is a diverse condition, classified into epithelial and non-epithelial types, with epithelial ovarian cancers (EOC) making up 90% of cases. The EOC is classified into subtypes: high- grade serous, low-grade serous, endometrioid, clear cell, and mucinous subtypes.[4,5]

Correspondence to: Dr. Namra Usman, Department of Community Health Sciences, The Aga Khan University, Karachi, Pakistan
E-mail: namra.usman22@alumni.aku.edu
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The endometrioid and mucinous subtypes of OC are less aggressive, diagnosed at an earlier stage, and associated with better survival compared to the high-grade serous subtype. Although the clear cell subtype is also high-grade, it tends to have better outcomes than high-grade serous cancers. However, studies have shown that advanced-stage mucinous and clear cell cancers can be aggressive and have lower survival rates than high-grade serous tumours.[6] Usually, low-grade serous and endometrioid types have the best survival rates irrespective of stages.[7] In a nomogram study, age, tumour location, preoperative CA125 levels, type of tumour cells, tumour severity, stage of cancer, surgical procedure, number of lymph nodes examined, size of any remaining tumour, and the spread of cancer to bones were identified as factors that could predict patient outcomes.[8] The prognosis for OC varies significantly based on the type of tumour, its location, and its stage of development.

OC is the second most common cancer among women in Pakistan,[3] yet there is insufficient research on this disease within the Pakistani population. Therefore, this study aimed to assess survival and identify factors associated with its out-comes and prognosis.

METHODOLOGY

This descriptive cohort study utilised retrospective data from 2010 to 2020, representing the period for which complete data abstraction was available. Inclusion criteria comprised women aged over 18 years with a biopsy-confirmed diagnosis of either EOC or non-epithelial ovarian cancer (non-EOC). Mortality data were updated during the data management process. Exclusion criteria included women aged under 18 years, those diagnosed with benign ovarian disorders, or those with a history of other malignancies. Patients lacking histological diagnostic information or those with incomplete data were excluded. OC cases were categorised in the cancer registry according to the International Classification of Diseases, Tenth Revision (ICD-10) and the World Health Organization classification into epithelial and non-epithelial types. Primary EOC subtypes were coded as follows: serous carcinoma (C56.0), endometrioid carcinoma (C56.1), clear cell carcinoma (C56.2), mucinous carcinoma (C56.3), transitional cell carcinoma (C56.4), and undifferentiated (NOS) carcinoma (C56.5). Non-EOC subtypes included malignant ovarian germ cell tumours (MOGCTs)/germ cell tumours (C56.6), sex cord-stromal tumours (SCSTs) (C56.7), and undifferentiated (NOS) forms, among others. Secondary OC (C56.8) was also included in the analysis. The ICD-O code for OC sites was C56.9.

Data on tumour characteristics, including histologic subtypes, grade, and cancer stage based on the American Joint Committee on Cancer (AJCC) system, were abstracted from the AKUH cancer registry. The study also examined treatment modalities such as chemotherapy, radiation, and surgical debulking procedures, which were further classified as complete (optimal) or incomplete (suboptimal) cytoreductive surgery. Sociodemographic and comorbidity data were extracted, encompassing age, marital status, employment status, city, family history of ovarian or other cancers, comorbidities, history of tobacco or alcohol use, and payment source. Additionally, information on CA-125 levels (categorised as normal <35 IU/mL or elevated >35 IU/mL) was also included. The primary outcome of interest was overall survival (OS), which is defined as the time from diagnosis to death or the study's conclusion. This study adhered to the STROBE guidelines for reporting observational studies, enhancing clarity, transparency, and reproducibility.

Categorical variables were presented as frequency counts and percentages. OS is calculated from the time of diagnosis to the last follow-up, and survival analysis was performed using Kaplan-Meier survival curves. Disease-free survival (DFS) is defined as the duration from the initiation of treatment for OC to the first occurrence of cancer recurrence or death. Significant factors identified in the univariate analysis ($p < 0.05$) were included in the multivariable analysis, which was conducted using the Cox proportional hazards model. The stepwise method with both backward elimination and forward addition of variables was carried out to achieve the final model with adjusted hazard ratio (HR) and 95% confidence interval (CI). The final model was adjusted for variables including age, stage, CA125, treatment modalities, types of cytoreductive surgery, chemotherapy, and cancer recurrence. Statistical analyses were performed using SPSS version 25 (IBM, New York, USA).

RESULTS

The survival analysis revealed an OS rate of 36.8%, with 1-, 3-, and 5-year rates of 89.8%, 84.4%, and 76.6%, respectively (Figure 1). DFS rates were 70.3%, 57.9%, and 36.6% at 1-, 3-, and 5-year, respectively, with a median DFS of 33 months.

Table I showed that age was significantly associated with survival, with patients >50 years demonstrating a higher HR (HR:1.57; CI: 1.18–2.09) compared to those aged ≤50 years. Residence in Karachi was also associated with an increased hazard of death (HR: 1.83; CI: 1.23–2.71). Other variables, including marital status, employment status, province, country, family history of ovarian or other cancers, tobacco use, and payment source, did not show statistically significant associations with survival. Alcohol consumption was notably rare in this cohort, with only 2 (0.2%) patients reporting a history of use. Therefore, no association between alcohol consumption and OC could be established.

In the univariate analysis of clinicopathological characteristics of OC patients in Karachi, Pakistan (Table II), histology was significantly associated with mortality risk ($p < 0.001$). EOC accounted for the majority of cases 93.4%. Among EOC subtypes, other histological types exhibited the highest HR for poor outcomes (HR: 4.80; CI: 2.18–10.6), followed by non-differentiated carcinoma (HR: 4.58; CI: 2.61–8.06). Clear cell carcinoma also demonstrated a substantially elevated risk (HR: 3.44; CI: 1.56–7.59). In terms of tumour size, tumours classified as T3 were the most frequent (51.6%) and were associated with increased risk (HR 2.26; CI: 0.99–5.13) compared to T0, which served as the reference category. Positive nodal involvement (N1), observed in 21.9% of patients, was linked to higher risk (HR 1.93; CI: 1.40–2.66) relative to node-negative (N0) cases. Patients with distant metastases had significantly elevated risk (HR 2.84; CI: 2.08–3.87) compared to those without metastases, while unknown metastasis status was also associated with poor outcomes (HR 3.59; CI: 1.47–8.78). The majority (86.9%) had unknown lymph vascular invasion status, while only 2.5% had confirmed lymph vascular invasion. No lymph vascular invasion was observed in 10.7% of cases. Due to the large proportion of missing data, no significant association between lymph vascular invasion and survival outcomes could be determined.

Advanced disease stages were associated with progressively higher risks. Stage 4 disease exhibited the highest risk (HR 6.38; CI: 3.93–10.36), followed by stage 3 (HR 3.26; CI: 2.05–5.18) and stage 2 (HR 3.08; CI: 1.50–6.33) compared to stage 1. Tumour grade was also a significant predictor, with undifferentiated or no specified grade tumours showing a higher risk (HR 1.78; CI: 1.12–2.85) relative to well and moderately differentiated tumours.

Table I: Univariate analysis of OC patients' sociodemographic characteristics, personal habits, and mode of payment residing in Karachi, Pakistan (n = 966).

Variables	n	%	Crude HR [95% CI]
Age (years)			
>50	501	51.9	1.57 (1.18 – 2.09)
≤50	465	48.1	Reference
Family history of OC			
Yes	42	4.3	0.69 (0.32 – 1.46)
No	924	95.7	Reference
Family history of other cancers			
Yes	228	23.6	0.85 (0.61 – 1.19)
No	738	76.4	Reference
History of tobacco use			
Yes	48	5.0	1.69 (0.98 – 2.91)
No	918	95.0	Reference
Payment source			
Out of pocket	855	88.5	1.38 (0.87 – 2.19)
Insured/Panel/Welfare	111	11.5	Reference

HR: Hazard ratio; CI: Confidence interval.

Table II: Univariate analysis of clinicopathological characteristics of OC patients in Karachi, Pakistan (n = 966).

Variables	n	%	Crude HR [95% CI]
Histology			
Non-EOC	58	6.6	
Sex cord stromal tumour	23	2.4	1.17 (0.39 – 3.58)
Germ Cell	35	3.6	1.31 (0.47 – 3.62)
EOC	908	93.4	
Serous carcinoma	326	33.7	1.67 (0.92 - 3.01)
Clear cell carcinoma	41	4.2	3.44 (1.56 – 7.59)
Mucinous carcinoma	63	6.5	1.16 (0.44 – 3.01)
Carcinoma (non-differentiated)	327	33.9	4.58 (2.61 – 8.06)
Other types	33	3.4	4.80 (2.18 – 10.60)
Endometrioid carcinoma	118	12.2	Reference
Tumour size			
TX	54	5.6	1.95 (0.75 – 5.09)
T3	498	51.6	2.26 (0.99 – 5.13)
T2	69	7.1	1.59 (0.61 – 4.14)
T1	316	32.7	0.85 (0.36 – 2.02)
T0	29	5.6	Reference
Nodes			
NX	89	9.2	1.26 (0.80 – 1.99)
N1	212	21.9	1.93 (1.40 – 2.66)
N0	665	68.8	Reference
Metastasis			
Unknown	13	1.3	3.59 (1.47 – 8.78)
Present	219	22.7	2.84 (2.08 – 3.87)
Not present	734	76.0	Reference
AJCC stage			
Unknown	77	8.0	2.59 (1.40 - 4.81)
Stage 4	219	22.7	6.38 (3.93 - 10.36)
Stage 3	374	38.7	3.26 (2.05 - 5.18)
Stage 2	46	4.8	3.08 (1.50 - 6.33)
Stage 1	250	25.9	Reference
Grade			
Unknown	691	71.5	1.78 (1.12 - 2.85)
Poorly differentiated	156	16.1	1.19 (0.66 - 2.14)
Well and moderately differentiated	119	12.3	Reference
Recurrence			
Never disease-free	336	34.8	18.14 (10.63 – 30.96)
Yes	298	30.8	7.12 (4.15 – 12.20)
No	332	34.4	Reference
CA-125 levels (IU/ml)			
Unknown	115	11.9	0.83 (0.44 - 1.56)
Abnormal (≥35)	744	77.0	1.28 (0.80 – 2.04)
Normal (<35)	107	11.0	Reference

*AJCC: American Joint Committee on Cancer; HR: Hazard ratio; CI: Confidence interval. **Others included Mullerian mixed tumour, malignant Brenner tumour, etc.*

Table III: Univariate analysis of the treatment modalities of OC patients in Karachi, Pakistan (n = 966).

Variables	n	%	Crude HR [95% CI]
Cytoreduction surgery status			
Not done	232	24.0	8.40 (5.99 - 11.78)
Suboptimal (R0 not achieved)	84	8.7	2.30 (1.48 – 3.56)
Optimal (R0 achieved)	650	67.3	Reference
Chemotherapy			
Done	750	77.6	0.51 (0.36 – 0.71)
Not done	216	22.4	Reference
Chemotherapy regimens			
Chemotherapy only	148	15.3	1.25 (0.82 – 1.90)
Adjuvant	320	33.1	0.34 (0.23 – 0.51)
Neo adjuvant	282	29.2	0.49 (0.33 – 0.73)
No chemotherapy done	216	22.4	Reference
Immunotherapy			
Done	38	3.9	1.22 (0.63 – 2.39)
Not done	928	96.1	Reference

HR: Hazard ratio; CI: Confidence interval.

Table IV: Multivariable Cox regression analysis of factors associated with OC survival in Karachi, Pakistan (n = 966).

Variables	*Adjusted HR [95% CI]
Cytoreduction surgery status	
No surgery done	3.94 (2.69 - 5.76)
Suboptimal (R0 not achieved)	2.01 (1.29 – 3.13)
Optimal (R0 achieved)	Reference
Chemotherapy	
Done	0.56 (0.39 – 0.82)
Not done	Reference
Recurrence	
Never disease-free	10.81 (6.12 - 19.07)
Yes	7.44 (4.31 - 12.86)
No	Reference

**Multivariable analysis using the multiple Cox proportional hazard regression adjusted for age, stage, CA-125, treatment modalities, cytoreductive surgery, chemotherapy, and recurrence.*

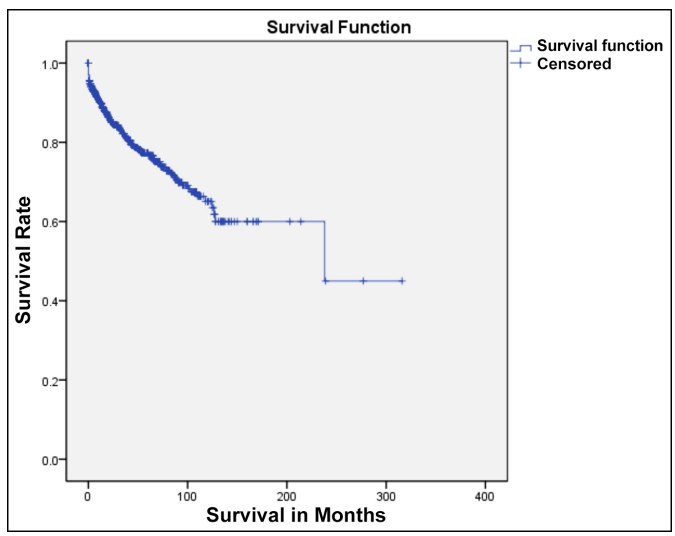

Figure 1: Kaplan-Meier survival curves of OC cases in Karachi, Pakistan.

Recurrence was the first reappearance of OC after the completion of first-line therapy. Patients who were never disease-free either had stage 4 disease at diagnosis or experienced disease progression despite treatment, thereby never achieving a disease-free status. Recurrence status was a strong prognostic factor. Patients who were never disease-free demonstrated

substantially elevated risk (HR 18.14; CI: 10.63–30.96) compared to recurrence-free patients, while those with recurrent disease also showed significantly higher risk of mortality (HR 7.12, CI: 4.15–12.20). Moreover, abnormal CA-125 levels (>35 IU/ml), which were present in 77% of cases, showed no significant increase in risk (HR 1.28; CI: 0.80–2.04) compared to normal levels (<35 IU/ml). These results underscore the prognostic significance of histology, tumour stage, grade, nodal involvement, recurrence status, and other clinical features in OC patients.

Table III presents the results of a univariate analysis evaluating the effect of treatment modalities on OC patients in Karachi, Pakistan. Based on surgical notes and margin status, cases were categorised as achieving or not achieving residual disease (R0). Optimal cytoreduction (R0 achieved) was performed in 67.3% of patients and served as the reference category for suboptimal surgery (R0 not achieved). Patients undergoing suboptimal cytoreduction had a significantly elevated risk (HR: 2.30; CI: 1.48–3.56), while those who did not undergo cytoreductive surgery demonstrated the highest risk (HR: 8.40; CI: 5.99–11.78). Additionally, over a decade, only 16 women underwent fertility-sparing surgery.

Chemotherapy was administered to 77.6% of patients and was associated with better survival (HR:0.51; CI: 0.36–0.71). Adjuvant chemotherapy alone showed the most protective effect (HR: 0.34; CI: 0.23–0.51). Neo-adjuvant chemotherapy also significantly reduced risk (HR: 0.49; CI: 0.33–0.73). The chemotherapy only group, which included patients receiving palliative chemotherapy, those treated at other institutions who came to AKUH solely for chemotherapy, patients lost to follow-up, and those with disease progression despite treatment, did not show any reduction in risk (HR: 1.25; CI: 0.82–1.90). These findings underscore the importance of chemotherapy regimens, particularly adjuvant approaches, in improving survival outcomes.

Immunotherapy was administered to only 3.9% of patients and did not demonstrate a significant difference in outcomes compared to those who did not receive it (HR: 1.22; CI: 0.63–2.39). Radiotherapy is not a standard treatment for OC and is typically reserved for selected patients with recurrence. Consequently, only 36 patients in the cohort received radiotherapy.

Table IV presents the results of the multivariable Cox regression analysis evaluating predictors of OC survival. Cytoreduction surgery status was a key determinant of survival outcomes. Patients who did not undergo surgery exhibited the highest risk (HR: 3.94; CI: 2.69–5.76), followed by those who underwent suboptimal cytoreduction (R0 not achieved; HR: 2.01; CI: 1.29 - 3.13), compared to those who underwent optimal cytoreduction (R0 achieved).

Chemotherapy was another significant predictor, with patients who received chemotherapy demonstrating a reduced risk of mortality (HR: 0.56; CI: 0.39–0.82) compared to those who did not receive chemotherapy.

Recurrence of disease strongly influenced survival, with patients who were never disease-free showing markedly elevated risk (HR: 10.81; CI: 6.12–19.07). Those who were never disease-free and those who experienced disease recurrence had poorer survival (HR:10.81; CI: 6.12 - 19.07 and HR: 7.44; CI: 4.31–12.86, respectively).

DISCUSSION

This study demonstrated a low five-year OS rate of 36.8%, which aligns with the findings reported in both global and regional literature. For instance, national data from the United Kingdom report a comparable five year OS rate of 31.0% for OC patients.[9] Regionally, a 2023 systematic review and meta-analysis by Maleki *et al*. examining OC survival across Asian countries reported pooled OS rates of 73.7% at one year, 61.3% at three years, and 59.6% at five years.[10] In the present study, the DFS rates were 70.3% at one year, 57.9% at three years, and 36.6% at five years, with a median DFS of 33 (IQR: 28.3–37.7 months). These results align with previous studies by Kurta *et al*. and Ebrahimi *et al*.[11,12]

This study reported poor survival outcomes in cases of disease recurrence, consistent with findings from other studies.[13-16] Recurrence remains a significant challenge in OC management, with approximately 70% of patients at risk of disease relapse.[17] A study conducted in Norway further highlighted that survival after recurrence is particularly poor, especially among women presenting with symptoms.[18] These findings reinforce the aggressive nature of OC and underscore the need for improved surveillance and therapeutic strategies to manage recurrence effectively.

Optimal cytoreduction, defined as achieving no macroscopic residual disease (R0), remains a cornerstone of OC treatment. R1 and R2 indicate macroscopic residual disease, with maximal diameters of <1 cm and >1 cm, respectively. These findings demonstrated that failure to achieve R0 or the absence of surgery significantly impacted the survival of OC patients. These results align with prior studies emphasising the importance of optimal cytoreduction.[19] Schwartz underscored the critical role of cytoreductive surgery in managing OC, demonstrating its impact on progression-free and OS.[20] Similarly, a meta-analysis by Chase *et al*. confirmed that the extent of residual disease strongly influences survival outcomes, highlighting the necessity of minimising residual disease during surgery.[21] Recent advances in OC treatment further support these findings. Kim *et al*. noted that even with evolving therapies, residual disease remains a key predictor of survival outcomes.[22] Furthermore, Chen concluded that achieving optimal cytoreduction consistently improves OS in OC patients, emphasising its importance regardless of treatment advancements.[23] These studies collectively affirm the significance of optimal cytoreduction, underscoring its critical role in improving outcomes for OC patients. This study's findings reinforce this perspective, emphasising the detrimental effect of suboptimal surgical outcomes on survival.

This study's finding of the effect of chemotherapy on better survival of OC is consistent with other research studies. Chemotherapy remains a cornerstone in the treatment of OC and is widely recognised as the global gold standard. Its critical role in improving survival outcomes is well-documented, particularly when combined with surgery and other therapeutic modalities. A meta-analysis by Kyrgiou *et al*. reinforces this study's findings, highlighting that chemotherapy, irrespective of the specific regimen, significantly enhances both progression-free and OS outcomes.[24] Recent advancements, such as hyperthermic intraperitoneal chemotherapy (HIPEC), have demonstrated promising results in prolonging survival for ovarian cancer patients.[25] However, the implementation of HIPEC remains limited in low- and middle-income countries (LMICs), including this study's centre, due to resource constraints. While studies emphasise the pivotal role of chemotherapy in extending survival, there is an urgent need to adopt innovative treatment modalities, such as HIPEC, to bridge the gap in treatment outcomes between high-income and resource-limited settings.

This study, while limited by its single-centre design and reliance on a hospital-based cancer registry due to the absence of a national registry, provides valuable insights into survival rates and prognostic factors for OC in Pakistani women. The hospital's cancer registry, which includes high-quality, standardised data from a diverse, nationwide patient population, was a key strength. However, the study faced challenges such as missing treatment data for many patients, particularly those lost to follow-up due to financial constraints. Another limitation of this study was that it could not differentiate between R1 and R2 but was able to determine whether R0 was achieved. Despite these limitations, the findings offer a baseline for future research and interventions, highlighting the importance of cancer registries in public hospitals and the need for a centralised national registry to improve early detection and survival outcomes, ultimately informing cancer control policies in Pakistan.

CONCLUSION

This study showed that cytoreductive surgery, various chemotherapy regimens, and recurrence were key determinants of survival among OC patients in Karachi. The study suggests that improving surgical outcomes, optimising chemotherapy, and enhancing early detection and recurrence monitoring are crucial steps for improving the survival of OC patients in Karachi.

ETHICAL APPROVAL:

Ethical approval was granted by the Ethical Review Committee of the Aga Khan University, Karachi, Pakistan (ERC ID# 10240).

PATIENTS' CONSENT:

Informed consent was not required, as all the data were anonymised. The study was conducted in compliance with the principles outlined in the Declaration of Helsinki.

COMPETING INTEREST:

The author declared no conflict of interest.

AUTHORS' CONTRIBUTION:

US, NU: Conceptualisation, ethical approval, methodology, investigation, data curation, validation, statistical analysis, manuscript writing, project administration, and supervision.
AT, UC: Subject expert, data interpretation, manuscript writing, editing, and review.
All authors approved the final version of the manuscript to be published.

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