

# Incidence and Prognostic Significance of Liver Metastases for Newly Diagnosed Ovarian Cancer in Relation to Subtypes

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## Research Article

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# Abstract

**Background:** Ovarian cancer is a heterogeneous and aggressive malignant tumor, and the liver is one of the most common metastases target visceral organs of ovarian cancer. We aim to analysis the incidence and prognostic relevance of histological subtypes for patients with liver metastases in newly diagnosed ovarian cancer. **Methods:** In the Surveillance, Epidemiology, and End Results (SEER) database, we identified the ovarian cancer patients from 2010 to 2016. Multivariable logistic regression was used to determine whether histological types were associated with the presence of liver metastases at diagnosis. The Kaplan-Meier method and multivariable Cox regression was performed to identify covariates associated with survival using the histological types. **Results:** Among 25293 ovarian cancer patients, 1749 cases presented with liver metastases. The incidence proportions were highest among ovarian carcinosarcoma patients (OR=17.76, 95% CI=9.26-34.09), and liver metastasis specificity was the highest in the clear cell type (70.69% of the metastatic subset). The median cancer-specific survival (CSS) for non-metastatic ovarian cancer patients was 77 months, but the ovarian cancer with only liver metastasis was 21 months. The mucinous (5 months; vs nonepithelial subtype, HR=0.26; 95% CI, 0.14-0.49) subtype experienced the shortest median survival among all histologic types. **Conclusion:** This population-based study provides that liver was one of the most common distant visceral organs for ovarian cancer metastasis, and the incidence proportions of liver metastasis were highest for carcinosarcomas subtype, and the mucinous ovarian cancer with liver metastasis being associated with the poorest survival.

## Background

Although ovarian cancer is an uncommon malignancy among females worldwide, it is the leading cause of death from gynecological cancers[1]. Largely driven by the lack of precise screening methods, approximately 70% of ovarian cancer patients are in an advanced stage (stage III and IV) at the initial diagnosis[2, 3]. Indeed, the 5-year cause-specific survival for all stages is 47%, compared with 89%, 71%, 41% and 20% for stages I, II, III and IV. Additionally, 26% of ovarian cancers are in stage IV at the time of diagnosis[4]. The definition of stage IV is the presence of distant organ metastasis excluding peritoneal metastases[5, 6]. And, more than a third of stage IV ovarian cancer experienced liver metastasis, which was the most common distant organ metastasis, followed by lung, bone, and brain metastasis[7]. However, the incidence and prognostic role of liver metastases in newly diagnosed ovarian cancer are poorly studied.

Ovarian cancer encompasses a heterogeneous group of malignancies that can be subdivided into different histological subtypes, and each subtype has different etiology, cell origin, clinical characteristics and therapeutic strategies. The histological subtypes include epithelial ovarian cancer (EOC) and non-epithelial ovarian cancer (NEOC)[8]. EOC accounts for more than 90% of ovarian cancers and include several morphological categories: serous, mucinous, endometrioid, clear cell, Brenner tumor, mixed, and undifferentiated[9, 10]. However, the understanding of the differences among those subtypes of ovarian cancer with liver metastasis remains poor.

This article was a population-based study using the Surveillance, Epidemiology, and End Results (SEER) database to provide an overview of liver metastasis at the initial ovarian cancer diagnosis, including the incidence and survival rates stratified by histopathological subtypes.

## Methods

### Patient Cohorts

Ovarian cancer cases were identified from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which is the largest publicly available cancer dataset. The SEER\*Stat software (version 8.3.4, <https://seer.cancer.gov/>) was used for demographic and clinical data collection. The ovarian cancer patients were extracted when they met all of the following criteria: 1) primary site recode ICD-O-3: C569 ovary, 2) behavior recode: malignant, and 3) diagnosed between 2010 and 2016. The exclusion criteria were as follows: 1) two or more primary cancers, 2) distant metastases unknown or not available (NA), and 3) stage information blank or NA. Finally, a total of 25293 cases were included in the finally analysis (**Figure 1**). This study was approved by the institutional review board of The Second Affiliated Hospital, Zhejiang University School of Medicine, and the need for written informed consent was waived.

Included patients were stratified by ICD-O-3 morphology codes for ovarian cancer histological types and grouped into nonepithelial ovarian cancer (e.g., germ cell, sex cord stromal), serous, mucinous, endometrioid, mixed, clear cell, carcinosarcoma, and neuroendocrinoid. Carcinoma, NOS, neoplasia and small groups (such as adenosquamous carcinoma and malignant Brenner tumors) were classified into the unknown group. Distant organ metastatic disease from ovarian cancer affected the liver, lung, bone and brain. A dichotomy was also applied for the histological grade to further classify serous ovarian cancer into high grade (grades 2, 3 and 4) and low grade (grade 1) disease.

## Statistical Analysis

Descriptive statistics including absolute number and incidence proportion were calculated to characterize the presentation for the patients with liver metastases at ovarian cancer initial diagnosis. The incidence proportion was estimated as the number of ovarian cancer patients diagnosed with liver metastases divided by the total number of ovarian cancer patients. Multivariable logistic regression was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) to quantify associations between histological types and the presence of liver metastases at diagnosis.

Survival analyses for ovarian cancer with or without liver metastasis were also calculated. The Kaplan-Meier curves and the log-rank test were utilized to compare survival between histologic subtypes and different stages. Multivariable Cox regression was performed to calculate adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) to identify covariates associated with survival using the histological types. These statistical analyses were conducted using SPSS software (version 19.0 IBM Corporation, Armonk, NY).

## Results

### Incidence of liver metastasis in ovarian cancer patients

There were 25293 ovarian cancer patients in the analyses, and 48.14%, 5.55%, 7.92%, 4.47.6%, 5.91%, 1.68%, 1.14% and 5.47% of those patients had the serous, mucinous, endometrioid, mixed, clear cell, carcinosarcoma and neuroendocrinoid types, respectively. For the cohort presented with distant organ metastases at any site (n = 2922), 44.90%, 2.49%, 2.09%. 2.19%, 1.98%, 3.42% and 1.44% had the serous, mucinous, endometrioid, mixed, clear cell, carcinosarcoma and neuroendocrinoid subsets, respectively. Of these, 1749 patients with liver metastases, showing 6.91% of the ovarian cancer population and 59.86% among the subset with metastatic disease at any site. **Table 1** have detailly presented the number and incidence proportions of liver metastases in newly diagnosed ovarian cancer, and stratified by ovarian cancer histological subtypes. The frequency of liver metastasis was

highest in ovarian carcinosarcoma patients (14.12% of the entire cohort). Among the subset with distant organ metastases, the proportion of those with liver involvement was approximately 60%, and liver metastasis specificity was the highest in the clear cell type (70.69% of the metastatic subset) and neuroendocrinoid carcinoma (71.43% of the metastatic subset) subtypes. For high- and low-grade serous ovarian cancer, the incidence proportion of liver metastases was significantly higher among those with high-grade serous ovarian cancer than among those with low-grade serous ovarian cancer (5.32% vs. 2.65% of the entire cohort) (**Table 2**). The influence of age and race is shown in **Supplementary Table 1**.

On multivariable logistic regression among metastatic ovarian cancer patients indicated that the serous (OR=7.94, 95% CI=4.37-14.43), mucinous (OR=3.68, 95% CI=1.88-7.18), endometrioid (OR=2.26, 95% CI=1.15-4.46), mixed (OR=4.23, 95% CI=2.15-8.32), clear cell (OR=3.45, 95% CI=1.77-6.74), carcinosarcoma (OR=17.76, 95% CI=9.26-34.09) and neuroendocrinoid (OR=13.06, 95% CI=6.47-26.36) subtypes, when compared with non-epithelial subtype. Ovarian carcinosarcomas was significantly greater odds of having liver metastases at initial diagnosis. More detail information and results are presented in **Table 3**.

### **Survival of liver metastasis in patients with ovarian cancer**

The median cancer-specific survival (CSS) for non-metastatic ovarian cancer patients was 77 months, but the CSS times for those with ovarian cancer with only liver metastasis was 21 months. The CSS times were 19 months, 18 months and 11 months for those with ovarian cancer with distant organ metastasis, liver metastasis and metastasis at  $\geq 2$  sites (including the liver) (**Figure 2**). Among the patients with different subtypes of ovarian cancer with only liver metastasis, those with nonepithelial (38 months) and serous ovarian cancer (33 months) experienced the longest median CSS, and patients with the mucinous (5 months) and neuroendocrinoid (6 months) subtypes experienced the shortest median survival (**Figure 3A**). The multivariate Cox regression analysis showed that patients with different subtypes were independently prognostic factor for CSS for liver metastatic ovarian cancer (**Table 4**). Mucinous (vs nonepithelial subtype; hazard ratio, 0.26; 95% CI, 0.14-0.49;  $P < 0.001$ ) subtype was significantly associated with decreased survival. Among those with serous ovarian cancer, high-grade ovarian cancer resulted in worse survival (vs low grade; hazard ratio, 0.34; 95% CI, 0.15-0.78;  $P < 0.001$ ) (**Figure 3B**).

Surgery is an important method of treatment for ovarian cancer. We found that the use of surgery was associated with a longer survival time compared with patients without surgery for ovarian cancer with only liver metastasis at the initial diagnosis ( $P < 0.001$ , **Supplementary Figure 1**). Interestingly, the survival time of non-metastatic ovarian cancer patients without surgery was shorter than that of ovarian cancer patients with liver metastasis who received surgery (HR=0.46, 95% CI=0.42-0.51).

## **Discussion**

Our study described the incidence proportion and prognostic role of liver metastasis in newly diagnosed ovarian cancer patients and the analyses also stratified by histologic subtypes. We observed that ovarian carcinosarcomas has the highest incidence of liver metastasis. Notably, the median cancer-specific survival significantly varied by different subtypes, ranging from 5 months in mucinous type to 34 months in nonepithelial ovarian cancer patients with liver metastasis. To the best of our knowledge, this is the first study to report population-based incidence proportions and survival outcomes stratified by histological subtypes in ovarian cancer patients with liver metastases on initial diagnosis.

In previously published study, Giovanni D. Aletti et al. evaluated on the incidence proportion of ovarian cancer patients who were in FIGO stage IV at the time of diagnosed from 1994 through 2003 at the Mayo clinic. They identified stage IV disease among 19% patients with ovarian cancer (all stages at diagnosis)[11]. The liver was the second most common metastasis site, accounting for 21% of the primary metastasis diagnosis and treatment. This study emphasized that stage IV is a heterogeneous ovarian cancer, and the metastases anatomic location at diagnosis appears useful as an excellent predictor for prognosis. Patients with liver metastases most frequently had recurrence and poor prognosis. As opposed to in this study, the tumor histological subtype was not available, and incidence was not reported. Our study focused on the cumulative incidence proportions of liver metastasis among patients with the different ovarian cancer subtypes. We found that the total incidence of ovarian cancer with liver metastasis was 6.91%, and carcinosarcoma of the ovary was the most common subtype among those with liver metastasis, accounting for 14.1%. Ovarian carcinosarcomas, also called malignant mixed Mullerian tumors (MMMTs), have been reported as a rare tumor with a poor prognosis[12, 13]. However, the liver metastasis of ovarian carcinosarcomas has not been described in previous published studies.

In a study of 1481 patients diagnosed with stage IV ovarian cancer, 32.5% had a single liver metastasis, and the median survival time was 30 months[7]. Another study in Japan, including 107 ovarian cancer patients, showed that the median ovarian survival was 9 months[14]. All the academic center-based retrospective studies suggested that ovarian cancer with liver metastasis predicted poor survival, and the median cancer-specific survival fluctuated between 8 and 40 months. We found that the median cancer-specific survival was obviously decreased in ovarian cancer patients with liver metastasis compared with those without metastasis (18 months vs. 77 months,  $P < 0.001$ ). When compared with distant visceral metastasis, there was no significant difference (18 months vs. 19 months,  $P < 0.81$ ). These data suggested that distant metastasis was the main cause of poor prognosis and that liver metastasis was still the most important factor. In addition, we also found that the median survival for ovarian cancer patients with liver metastases varied significantly by histological subtype, with mucinous ovarian cancer being associated with the worst survival (median cancer-specific survival, 4 months). Serous ovarian cancer patients had the longest survival (median cancer-specific survival, 21 months).

Due to the low level and small-scale studies, the professional guidelines did not recommend the treatment of liver metastasis of ovarian cancer[15-17]. Several studies have suggested that surgery for liver resection for ovarian cancer with liver metastasis predicts a favorable prognosis compared to women with unresectable liver disease[18-20]. Our data also showed the same results. Therefore, liver surgery, especially R0 surgery, should be recommended for ovarian cancer with liver metastasis. Certainly, new therapeutic approaches, including radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE), all have appeared to have therapeutic effects in small sporadic samples or case studies[21, 22].

Our study should be considered in the context of its limitations. First, 25293 cases of ovarian cancer from SEER database were included in this study, although the SEER data covers approximately 30% of the United States population, the selection bias was inevitable in the incidence proportions analysis. Second, the SEER database did not provide information about ovarian cancer recurrence, so we only described liver metastases at initial diagnosis. Third, information from SEER database did not provide chemotherapy data, so the chemotherapy-related prognostic analyses for liver metastasis were not conducted.

## Conclusion

This study provides new insight into the epidemiology and clinicopathological features of liver metastases at the initial diagnosis of ovarian cancer. Liver was one of the most common distant visceral organs for ovarian cancer metastasis, and the incidence proportions of liver metastasis were highest among patients with carcinosarcomas subtype, with the mucinous ovarian cancer with liver metastasis being associated with the poorest survival. These data will help prioritize future research directions, especially for liver metastasis screening and therapy.

## Abbreviations

SEER: Surveillance, Epidemiology and End Results; ICD-O-3: International Classification of Diseases in Oncology, third edition; CSS: Cancer-specific Survival; ORs: Odds Ratios; 95% CIs: 95% Confidence intervals; HRs: Hazard Ratios; EOC: Epithelial Ovarian Cancer; NEOC: Non-epithelial Ovarian Cancer; MMMTs: malignant mixed Mullerian tumors; RFA: Radiofrequency Ablation; TACE: Transcatheter Arterial Chemoembolization.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Availability of data and materials*

Data was publicly available in the SEER database.

### *Competing interests*

No potential conflicts of interest were disclosed.

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### *Authors' contributions*

Ying Zhu and Zhigang Zhang: Data analysis, critical review of the manuscript, and drafting of the manuscript. Yifang Zhang: Data analysis and drafting of the manuscript. Lingyun Zhai: Acquisition of data from the Surveillance, Epidemiology, and End Results database. Jianwei Zhou: Study design and data analysis

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## Tables

**Table 1. Incidence Proportion and Median Survival of Ovarian Cancer with Liver Metastasis by Subtype**

Subtype		Patients, No.			Incidence Proportion of Liver Metastases, %		Survival Among Patients with Liver Metastases, Median (months)
		With Ovarian Cancer	With Metastatic Disease	With Liver Metastases	Among Entire Cohort	Among Subset with Metastatic Disease	
Total		25293	2922	1749	6.91	59.86	18
Epithelial	Serous	12175	1312	768	6.31	58.54	33
	Mucinous	1403	73	41	2.92	56.16	5
	Endometrioid	2003	61	36	1.80	59.02	23
	Mixed	1130	64	38	3.36	59.38	23
	Clear cell	1496	58	41	3.88	70.69	9
	Carcinosarcoma	425	100	60	14.12	60	14
	Neuroendocrinoid	289	42	30	10.38	71.43	6
Non-epithelial		1384	41	31	2.96	75.61	38
Unknown		4988	1171	704	14.11	60.12	7

**Table 2. Incidence Proportion of Serous Ovarian Cancer with Liver Metastasis by Grade**

Variable	Patients, No.		Incidence Proportion of Liver Metastases Among Entire Cohort, %
	Patients (N=12175)	With Liver Metastases (N=768)	
Low grade*	340	9	2.65
High grade**	8860	471	5.32
Unknown	2975	288	9.68
*Grade 1; **Grade 2, 3, or 4			

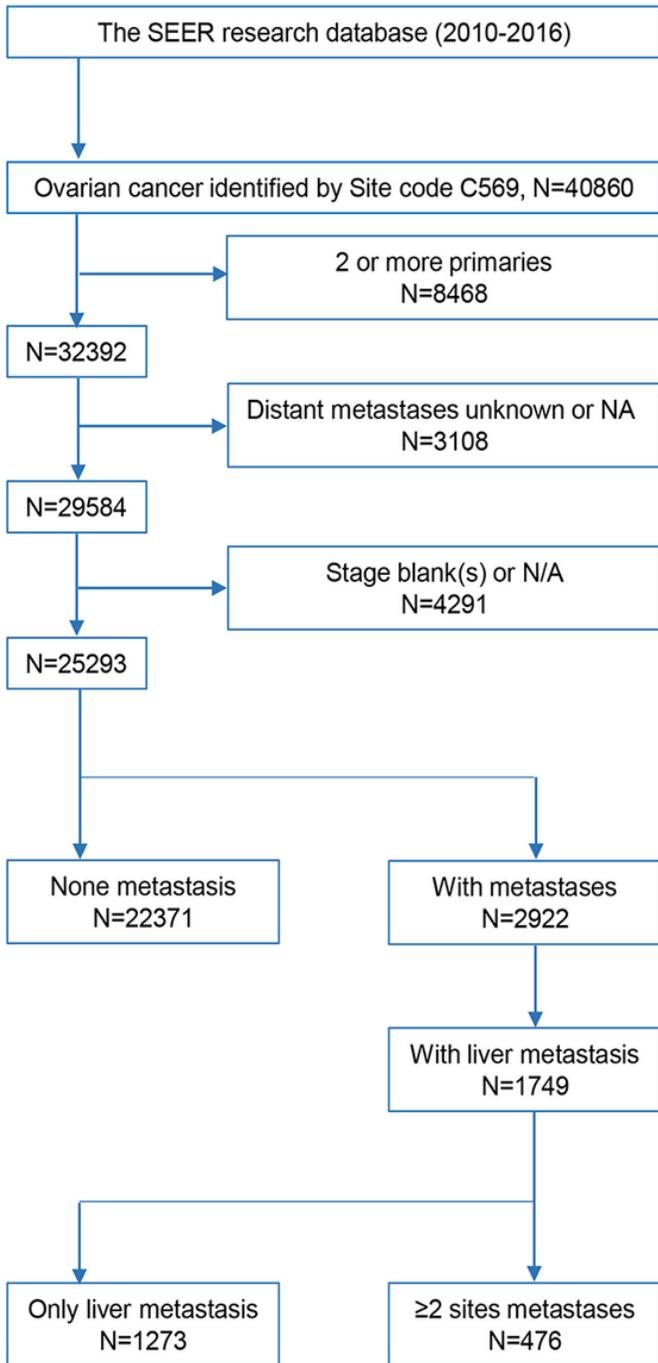
**Table 3. Multivariable Logistic Regression for Ovarian Cancer with Liver Metastasis by Different subtypes**

Variable	Distant Organ Metastases Among Entire Cohort		Liver Metastasis Among Entire Cohort		
	OR (95% CI)	P Value	OR (95% CI)	P Value	
Non-epithelial	1 [Reference]	NA	1 [Reference]	NA	
Epithelial	Serous	3.64 (2.65-4.99)	<0.001	7.94 (4.37-14.43)	<0.001
	Mucinous	1.76 (1.19-2.59)	0.005	3.68 (1.88-7.18)	<0.001
	Endometrioid	1.03 (0.69-1.54)	0.893	2.26 (1.15-4.46)	0.018
	Mixed	1.91 (1.28-2.85)	0.001	4.23 (2.15-8.32)	<0.001
	Clear cell	1.31 (0.87-1.97)	0.195	3.45 (1.77-6.74)	<0.001
	Carcinosarcoma	7.94 (5.44-11.61)	<0.001	17.76 (9.26-34.09)	<0.001
	Neuroendocrinoid	4.91 (3.13-7.68)	<0.001	13.06 (6.47-26.36)	<0.001
Unknown	7.93 (5.77-10.88)	<0.001	17.76 (9.76-32.01)	<0.001	
OR: odds ratio. NA: not available.					

**Table 4. Multivariable Cox Regression for overall survival Among Ovarian Cancer with Liver Metastases**

Variable		HR (95% CI)	P Value
Non-epithelial		1 [Reference]	NA
Epithelial	Serous	0.97 (0.6-1.58)	0.91
	Mucinous	0.26 (0.14-0.49)	<0.001
	Endometrioid	0.94 (0.49-1.79)	0.85
	Mixed	0.71 (0.38-1.32)	0.28
	Clear cell	0.39 (0.21-0.71)	0.002
	Carcinosarcoma	0.45 (0.25-0.81)	0.007
	Neuroendocrinoid	0.34 (0.18-0.63)	0.001
Unknown		0.33(0.19-0.54)	<0.001
HR: Hazard Ratio. NA: not available.			

## Figures



**Figure 1**

The flowchart for ovarian cancer patients from the SEER database in this study

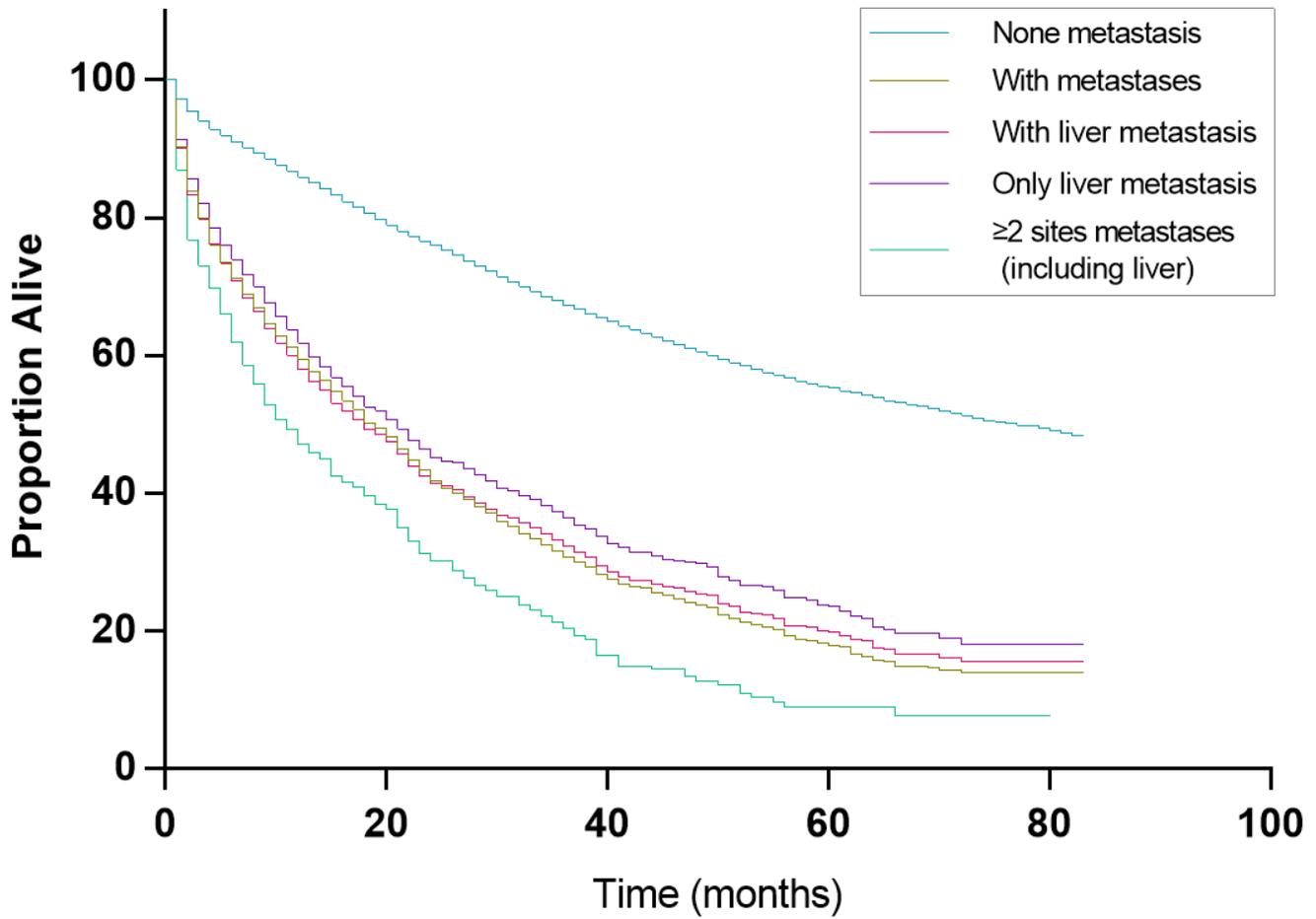
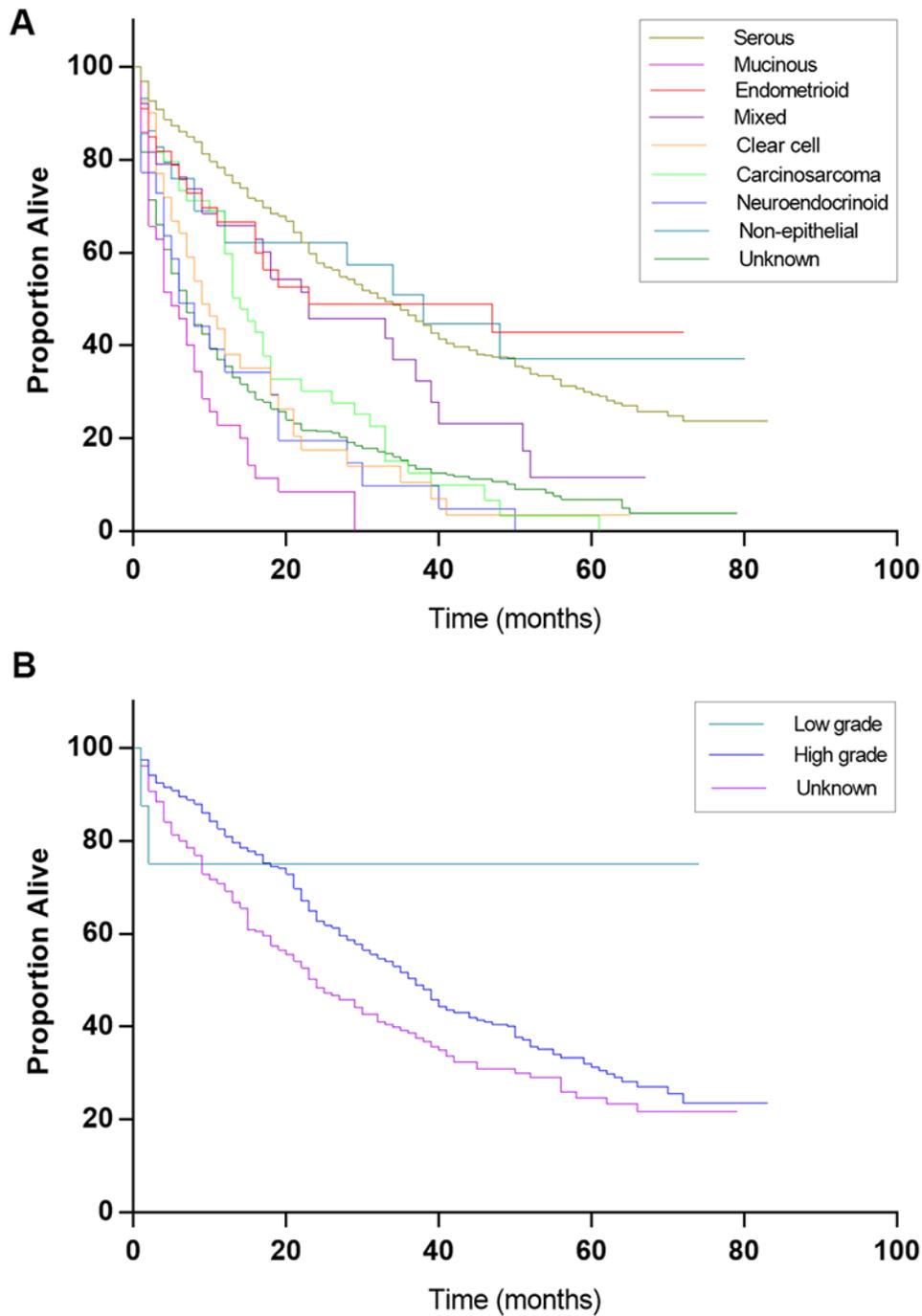


Figure 2

Cancer-specific survival among ovarian cancer patients with or without metastasis at diagnosis



**Figure 3**

Cancer specific survival among the ovarian cancer patients with liver metastasis, 3A. Cancer specific survival among the ovarian cancer patients with liver metastasis by histopathological types, 3B. Cancer-specific survival among serous ovarian cancer patients with liver metastasis by histological grade

## Supplementary Files

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