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Characteristics, Treatment and Outcomes of Women with Immature Ovarian Teratoma, 1998–2012

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Abstract

Objective—To explore the presentation, management and outcomes of adult women diagnosed with immature ovarian teratoma.

Methods—The National Cancer Database (NCDB) was used to identify women 18 years of age diagnosed with an immature teratoma from 1998–2012. We analyzed demographic, clinical and tumor characteristics, and treatment trends. Multivariable models were employed to examine predictors of adjuvant chemotherapy use and survival.

Results—We identified a total of 1045 adult women with immature teratoma. The median age of diagnosis was 27 years and most were diagnosed between ages 18 and 39 (88.9%). The majority presented with early-stage (I/II) disease (76.0%), underwent unilateral salpingo-oophorectomy (52.5%) and received adjuvant chemotherapy (56.8%). The probability of receiving chemotherapy increased with stage, grade, and treatment at academic compared to community based centers ($P < 0.05$). Older age, advanced stage, and grade III histology were associated with worse survival ($P < 0.05$). Five-year survival rates were: 98.3% (95% CI 96.8–99.1), 93.2% (95% CI 82.8–97.4), 82.7% (95% CI 74.3–88.5), and 72.0% (95% CI 50.1–85.5) for stages I, II, III, and IV disease, respectively.

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Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Conclusions—The incidence of immature teratoma is highest in young adults aged 18 to 39. Most patients present with early-stage disease, are managed with fertility sparing surgery and chemotherapy and have an excellent prognosis. Later age at diagnosis, advanced stage, and high-grade histology confer a worse prognosis.

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare, accounting for fewer than 5% of all malignant ovarian neoplasms, [1, 2] with a cumulative 30-year, age-adjusted incidence rate of 0.34 per 100,000 woman-years. [2] Among MOGCTs, dysgerminomas and immature teratomas are the most common histologic subtypes, with immature teratomas accounting for 35–38% of cases. [2, 3] Immature teratomas consist of tissue derived from the three germ layers and contain immature neural elements. The quantity of immature neural tissue alone determines the grade. [4] Therapy consists of unilateral salpingo-oophorectomy with wide sampling of peritoneal implants. If the tumor is confined to the ovary and grade I, no further therapy is needed. However, chemotherapy is recommended for higher grade and stage disease. [5] Treatment with surgery followed by systemic chemotherapy can achieve remission and cure in over 90% of cases. [3, 4]

Due to their rarity, data on immature ovarian teratomas are limited. Most population-based studies have examined MOGCTs as a group [2, 3, 6], while those studies focusing on immature teratomas have consisted of small, retrospective single-institution series. [4, 7] Additionally, many studies have looked exclusively at the pediatric and adolescent population. [8–10] Little is known about the nationwide patterns of care and outcomes of immature ovarian teratomas as a specific histology and in adult women. Therefore, we performed a population-based analysis to examine the demographic and clinical characteristics, treatments, survival rates, and prognostic indicators of patients presenting with immature teratoma.

Materials and Methods

Patient-level data from the National Cancer Data Base (NCDB) were used for analysis. NCDB is a nationwide registry developed by the American College of Surgeons and the American Cancer Society. [11, 12] NCDB records all patients with newly diagnosed invasive tumors from more than 1,500 Commission on Cancer-affiliated hospitals from throughout the United States, capturing approximately 70% of all newly diagnosed cancers nationwide. The database includes information on patient demographics, tumor characteristics, treatment data, staging, follow-up and survival. Data are abstracted by trained cancer registrars, are audited regularly, and have been utilized in a large number of outcomes studies. The data do not contain patient identifiers and the study was deemed exempt by the Columbia University Institutional Review Board. We included in this study women ages 18 and older who were diagnosed with immature teratoma of the ovary at any FIGO stage between the years 1998 and 2012. Patients with mixed germ cell tumor histology and those with benign or borderline tumors were excluded.

Demographic data analyzed included age (18–19, 20–29, 30–39, 40–49, 50 years), race and ethnicity (white, black, Hispanic, other, unknown), insurance status (uninsured, private insurance, Medicaid, Medicare, other, unknown), income (<\$30,000; \$30,000–\$34,999; \$35,000–\$45,999; \$46,000+; unknown as determined by the median household income in the patient's zip code) and education (percentage of adult residents in a patient's zip code that did not graduate from high school, categorized as equally proportioned quartiles among all US zip codes). Comorbidity was estimated using the Deyo classification of the Charlson comorbidity score (0, 1, 2). [13, 14] Hospital characteristics that were analyzed included geographic region and location (metropolitan, urban, rural, unknown). Hospitals were classified as academic or research cancer programs, comprehensive community cancer programs (accessing 500 or more cancer patients per year) or community cancer programs (accessing more than 100 but fewer than 500 cancer patients per year) based on the American College of Surgeon's Commission on Cancer Criteria.[12] Tumor data analyzed included grade (1, 2, 3, unknown) and FIGO stage. If pathologic stage was known, this value was used for analysis. If pathologic stage was unknown, clinical stage was used. If neither pathologic nor clinical stage were known, the tumor was reported as unstaged. Due to the small number of women with stage IB tumors, stages IB and IC neoplasms were classified together. Treatment data analyzed included type of surgery performed (unilateral oophorectomy, bilateral oophorectomy, oophorectomy plus omentectomy, tumor debulking or unknown), whether lymphadenectomy was performed, lymph node status if known, and whether chemotherapy was administered. The percentage of patients receiving chemotherapy was further stratified by stage and grade.

Multivariable generalized estimating equations with a Poisson distribution and log link function were developed to examine predictors of chemotherapy while controlling for other clinical, demographic, and hospital characteristics. Results are reported as adjusted risk ratios (aRR) with 95% confidence intervals. All-cause mortality was estimated as the number of months from the date of diagnosis until death from any cause. Patients alive at the last follow-up were censored. Marginal Cox proportional hazards models that account for hospital clustering were developed to estimate predictors of mortality. Results are reported as adjusted hazard ratios (aHR) with 95% confidence intervals. Five-year survival rates are reported descriptively, stratified by stage, with 95% confidence intervals. Kaplan-Meier curves for overall survival by stage are depicted. The log-rank test was used to compare the survival distributions between stages. All hypothesis tests were two-sided. A P-value of < .05 was considered statistically significant. All analyses were conducted using SAS version 9.4.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the cohort are presented in Table 1. A total of 1045 women were identified. The median age at diagnosis was 27 (range 18–84) and the majority were of reproductive-age (88.9% between ages 18 and 39). At the time of diagnosis, 76% of patients had early stage (I/II) disease. The majority of patients underwent fertility sparing surgery consisting of unilateral salpingo-oophorectomy (52.5%).

Lymphadenectomy was performed in fewer than half of the patients (47.7%), and the nodes were positive in 6.8% of those sampled.

Use of Chemotherapy

A total of 594 (56.8%) women received adjuvant chemotherapy. Stratified by stage, 50.1% of stage I, 79.4% of stage II, 84.6% of stage III and 80.0% of stage IV patients received adjuvant chemotherapy. Stage I patients were further stratified by sub-stage and grade: 5.3% of stage IA/grade I patients received adjuvant chemotherapy compared to 73% of stage IA / grade 2–3 patients, 51.9% of stage IB–IC/grade I patients, and 78% of stage IB–IC/grade 2–3 patients. Patients with stage IA/grade I tumors had significantly lower rates of chemotherapy than any other stage/grade pair ($p<0.001$).

Predictors of chemotherapy use are summarized in Table 2. After adjusting for other demographic and clinical characteristics, the likelihood of chemotherapy increased with higher stage (aRR 1.40; 95% CI, 1.22–1.61 for stage IB–IC; aRR 1.62; 95% CI, 1.39–1.90 for stage II; aRR 1.53; 95% CI, 1.36–1.71 for stage III; aRR 1.51; 95% CI, 1.20–1.88 for stage IV) and with higher tumor grade (aRR 3.52; 95% CI, 2.62–4.73 for grade II tumors; aRR 3.98; 95% CI, 2.99–5.30 for grade III). Additionally, women treated at academic/research centers were more likely to receive chemotherapy (aRR 1.39; 95% CI, 1.08–1.79), while those >50 years of age were less likely to receive treatment with chemotherapy (aRR 0.60; 95% CI, 0.40–0.91) ($P<0.05$ for all comparisons).

Survival

Advanced stage was the strongest predictor of survival (Table 3). Compared to women with stage I tumors, the adjusted hazard ratio for death increased to 3.37 (95% CI, 1.12–10.17) for stage II tumors, 8.26 (95% CI, 3.18–21.45) for stage III tumors and 29.49 (95% CI, 9.30–93.53) for stage IV cancers. Similarly, the adjusted hazard ratio for death for poorly differentiated (compared to well differentiated tumors) was 8.07 (95% CI, 2.13–30.61). Older women (> 50 years of age) had an increased mortality rate (aHR=21.76; 95% CI, 4.96–95.43) compared to the youngest age cohort (18–19). Race and year of diagnosis were not associated with prognosis. Five-year survival was 98.3% (95% CI, 96.8–99.1%) for stage I tumors (Table 4). When stratified by sub-stage, survival at 5 years was 98.7% (95% CI, 96.7–99.4%) for stage IA and 97.1% (95% CI, 91.0–99.1%) for stage IB–C tumors.

Five-year survival was 93.2% (95% CI, 82.8–97.4%) for stage II cancer, 82.7% (95% CI, 74.3–88.5%) for stage III malignancies, and 72.0% (95% CI, 50.1–85.5%) for stage IV tumors. Figure 1 displays Kaplan-Meier survival curves for the cohort. The median follow-up time was 61.6 months.

Discussion

We found that the incidence of immature teratomas is highest in women ages 18 through 39 and that most patients present with early-stage disease. Fertility sparing surgery and chemotherapy are the mainstays of therapy. Survival rates are excellent across stages, but older age at diagnosis, advanced stage, and high grade histology are associated with increased mortality.

The most important prognostic indicator was stage at presentation (HR 3.37, 8.26, 29.49 for stages II, III, IV respectively). This is in concordance with prior studies which have shown a significant positive association between stage and mortality,[6, 15, 16] Advanced stage was also positively correlated with likelihood of receiving chemotherapy.

In spite of the prognostic significance of stage, fewer than half of patients underwent a staging lymphadenectomy, and only a quarter underwent omentectomy, both of which are recommended by the National Comprehensive Cancer Network (NCCN) as part of comprehensive surgical staging of malignant ovarian germ cell tumors in adult patients. [5] The decision not to pursue full staging may be explained by the overall good prognosis of these tumors across stages and by the fact that staging may not affect management, as evidenced by the high prevalence of chemotherapy use across stages.

Grade was another important prognostic factor in this study, with poorly differentiated tumors associated with a hazard ratio for mortality of 8.07 compared to well differentiated tumors. Although we could not compare survival rates stratified by stage and grade due to the low number of deaths in each group, we did find significant differences in the rates of chemotherapy between those with stage IA, well differentiated tumors (5.3%) and all other stage/grade combinations (50%). This is in keeping with NCCN guidelines which recommend surveillance for patients with stage I dysgerminomas and stage I, grade I immature teratomas based on studies in the pediatric population. [5, 17]

Age greater than 50 years was a negative prognostic indicator when compared to 18–19 years of age, although this may be driven by age-associated comorbidities not fully captured in the multivariable model. Other studies have found either a modest [18] or no association between age at presentation and survival. [15, 16] Interestingly, women over 50 were less likely to receive chemotherapy even when controlling for tumor characteristics and other clinical variables. It is possible that differences in treatment strategies may be driving, at least in part, the increased mortality.

A recent study examining NCDB data [3] found an independent association between African American race and higher mortality rates from advanced stage (III/IV) MOGCTs. However, when looking specifically at immature teratomas, we did not find race to be a significant prognostic factor. This discrepancy may be explained by the prior study's reliance on a mixed pool of all MOGT histologies; the prognostic value of race may have been driven by the unequal racial distribution of dysgerminomas (which are more prevalent in whites and carry a more favorable prognosis) and immature teratomas (which are more prevalent in black women and carry a worse prognosis). When we examined immature teratomas separately, there was no association between race and mortality

We found that the majority of women underwent unilateral oophorectomy (52.5%). Given the nature of the database, it is not possible to elucidate exactly whether those women who underwent “oophorectomy and omentectomy” had unilateral or bilateral oophorectomies, though it is likely that a significant proportion of these were USOs with omentectomy performed for staging purposes; thus, the true prevalence of fertility-sparing surgery may be even higher. A SEER database study that examined treatment trends between 1988–2001

previously showed that the use of fertility-sparing surgery was increasing, from 40.5% in 1988–1992 to 48.4% between 1998–2001 [6]; our data from 1998–2012 would suggest this trend continues, though a direct comparison is not possible.

The majority of women received chemotherapy except for those with stage IA/grade I disease. Additionally, younger women were more likely to receive chemotherapy. Given the fertility-sparing surgical intent, it is important to ascertain to what extent provision of chemotherapy undermines this goal. These data are not available from the NCDB, but other studies suggest favorable reproductive outcomes. [19–22] As these studies are based on small patient series, further outcomes research on this topic to confirm reproductive safety would be of value.

We recognize several important limitations to these data. The data collected comes from varied institutions without centralized pathology review and thus we cannot exclude the possibility that some tumors were misclassified. Additionally, the data have limited granularity and certain clinical details are lacking (for instance, status of serum tumor markers, specific surgery performed, adequacy of surgical staging, presence of residual disease, number of cycles of chemotherapy received, chemotherapeutic regimens used, and degree of response to chemotherapy are not known). Further, although our study included a large sample, some of the sub-stages had limited numbers of women. Despite these limitations, this study is among the largest population-based studies of this rare form of cancer to date.

In summary, this study reflects the epidemiologic trends in the presentation, management, and outcomes of women with immature ovarian teratoma. Given its peak incidence in young women and excellent prognosis, future research should focus on preservation of hormonal and reproductive function in women treated for immature ovarian teratoma.

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Research Highlights

- The incidence of immature teratoma is highest in young adults aged 18 to 39.
- Most patients present with early-stage disease, are managed with fertility sparing surgery and chemotherapy and have an excellent prognosis.
- Later age at diagnosis, advanced stage, and high-grade histology confer a worse prognosis.

Follow-up month		12	24	36	48	60	72	84	96	108	120
IA	N died	1	1	2	0	1	1	1	1	1	0
	N alive	455	430	374	374	268	221	197	164	114	114
IB-IC	N died	0	1	1	1	0	0	1	0	0	0
	N alive	137	123	109	79	79	79	40	40	40	40
INOS	N died	0	1	0	0	0	0	0	0	0	0
	N alive	69	63	63	63	63	63	63	63	63	63

Figure 1.
Kaplan-Meier analysis of survival for women with stage I (Figure 1A) and stages II–IV (Figure 1B) immature teratoma.

Table 1

Demographic and clinical characteristics of patients with immature teratoma.

	N	%
<i>Age</i>		
18–19	124	(11.9)
20–29	491	(47.0)
30–39	314	(30.1)
40–49	75	(7.2)
50	41	(3.9)
<i>Race</i>		
White	593	(56.8)
Black	206	(19.7)
Hispanic	157	(15.0)
Other	73	(7.0)
Unknown	16	(1.5)
<i>Insurance status</i>		
Private	700	(67.0)
Medicare	23	(2.2)
Medicaid	158	(15.1)
Uninsured	112	(10.7)
Other	20	(1.9)
Unknown	32	(3.1)
<i>Income</i>		
< \$30,000	155	(14.8)
\$30,000–\$34,999	157	(15.0)
\$35,000–\$45,999	282	(27.0)
\$46,000+	399	(38.2)
Unknown	52	(5.0)
<i>Education</i>		
≥29%	226	(21.6)
20–28.9%	208	(19.9)
14–19.9%	201	(19.2)
<14%	358	(34.3)
Unknown	52	(5.0)
<i>Facility type</i>		
Community cancer	82	(7.9)
Comprehensive community cancer	491	(47.0)
Academic/research	471	(45.1)
Other	*	*
<i>Facility region</i>		
Eastern	219	(21.0)
Midwest	307	(29.4)

	N	%
South	305	(29.2)
West	214	(20.5)
<i>Facility location</i>		
Metropolitan	885	(84.7)
Urban	96	(9.2)
Rural	10	(1.0)
Unknown	54	(5.2)
<i>Comorbidity (Charlson/Deyo)</i>		
0	755	(72.3)
1	47	(4.5)
2	*	*
Unknown	238	(22.8)
<i>Year of diagnosis</i>		
1998	39	(3.7)
1999	49	(4.7)
2000	34	(3.3)
2001	46	(4.4)
2002	70	(6.7)
2003	72	(6.9)
2004	77	(7.4)
2005	82	(7.9)
2006	75	(7.2)
2007	87	(8.3)
2008	73	(7.0)
2009	84	(8.0)
2010	88	(8.4)
2011	86	(8.2)
2012	83	(7.9)
<i>Stage</i>		
IA	502	(48.0)
IB–IC	147	(14.1)
INOS	77	(7.4)
II	68	(6.5)
III	143	(13.7)
IV	25	(2.4)
Unknown	83	(7.9)
<i>Grade</i>		
Well	231	(22.1)
Moderate	249	(23.8)
Poorly	387	(37.0)
Unknown	178	(17.0)
<i>Surgery</i>		

	N	%
None	10	(1.0)
USO	549	(52.5)
BSO	97	(9.3)
Ovary/Omentectomy	286	(27.4)
Debulking	92	(8.8)
Unknown	11	(1.1)
<i>Regional nodes examined</i>		
Yes	498	(47.7)
No	526	(50.3)
Unknown	21	(2.0)
<i>Regional nodes positive^I</i>		
Positive	34	(6.8)
Negative	462	(92.8)
Unknown	*	*
<i>Chemotherapy</i>		
Yes	594	(56.8)
No	405	(38.8)
Unknown	46	(4.4)

^I Among patients that had regional nodes examined.

* Censored due to small sample size.

Table 2

Predictors of chemotherapy use in women with immature teratoma.

	aRR
<i>Age</i>	
18–19	Referent
20–29	1.11 (0.96–1.29)
30–39	1.08 (0.92–1.26)
40–49	0.93 (0.74–1.17)
50	0.60 (0.40–0.91) *
<i>Race</i>	
White	Referent
Black	1.03 (0.91–1.17)
Hispanic	1.03 (0.90–1.18)
Other	1.15 (0.96–1.38)
Unknown	1.15 (0.89–1.48)
<i>Insurance status</i>	
Private	Referent
Medicare	1.06 (0.70–1.59)
Medicaid	1.11 (0.99–1.24)
Other Government	1.10 (0.86–1.41)
Uninsured	1.10 (0.95–1.28)
Unknown	0.81 (0.51–1.28)
<i>Income</i>	
<\$30,000	Referent
\$30,000–\$34,999	0.98 (0.84–1.14)
\$35,000–\$45,999	1.03 (0.89–1.18)
\$46,000+	0.97 (0.83–1.13)
Unknown	1.07 (0.80–1.44)
<i>Facility type</i>	
Community cancer	Referent
Academic/research	1.39 (1.08–1.79) *
Comprehensive community cancer	1.30 (1.01–1.67) *
Other	1.55 (1.04–2.28) *
<i>Facility region</i>	
Eastern	Referent
Midwest	0.91 (0.79–1.05)
South	1.04 (0.91–1.19)
West	0.90 (0.78–1.05)
<i>Facility location</i>	
Metropolitan	Referent
Urban	0.98 (0.86–1.13)

aRR	
Rural	1.19 (0.94–1.49)
Unknown	0.97 (0.73–1.30)
<i>Year of diagnosis</i>	
1998	Referent
1999	1.07 (0.80–1.45)
2000	1.15 (0.82–1.61)
2001	1.01 (0.72–1.41)
2002	1.00 (0.73–1.36)
2003	1.02 (0.76–1.38)
2004	1.07 (0.79–1.43)
2005	0.95 (0.70–1.29)
2006	1.04 (0.78–1.38)
2007	1.15 (0.88–1.52)
2008	0.94 (0.70–1.24)
2009	0.94 (0.70–1.25)
2010	0.97 (0.73–1.30)
2011	0.80 (0.58–1.09)
2012	0.96 (0.71–1.30)
<i>Stage</i>	
IA	Referent
IB–IC	1.40 (1.22–1.61) *
INOS	0.98 (0.78–1.23)
II	1.62 (1.39–1.90) *
III	1.53 (1.36–1.71) *
IV	1.51 (1.20–1.88) *
Unknown	0.97 (0.80–1.18)
<i>Grade</i>	
Well	Referent
Moderate	3.52 (2.62–4.73) *
Poorly	3.98 (2.99–5.30) *
Unknown	2.57 (1.89–3.48) *

aRR: Adjusted risk ratio (95% confidence interval).

46 patients with unknown chemotherapy were excluded. Age, race, insurance status, income, facility type, region, location, year of diagnosis, stage and grade were included in the generalized estimating equations accounting for facility-level clustering.

* P<0.05.

Table 3

Multivariable model of predictors of mortality.

	aHR
<i>Age</i>	
18–19	Referent
20–29	0.87 (0.25–2.96)
30–39	0.62 (0.16–2.39)
40–49	0.46 (0.07–3.11)
50	21.76 (4.96–95.43) *
<i>Race</i>	
White	Referent
Black	1.52 (0.56–4.10)
Hispanic	0.40 (0.13–1.25)
Other	0.57 (0.19–1.72)
Unknown	4.71 (0.41–54.44)
<i>Insurance status</i>	
Private	Referent
Medicare	0.52 (0.14–1.91)
Medicaid	1.54 (0.49–4.81)
Uninsured	2.72 (0.97–7.61)
Other	— [†]
Unknown	4.73 (1.29–17.31) *
<i>Income</i>	
< \$30,000	Referent
\$30,000–\$34,999	0.78 (0.24–2.53)
\$35,000–\$45,999	1.04 (0.41–2.62)
\$46,000+	1.08 (0.37–3.18)
Unknown	3.78 (0.52–27.76)
<i>Facility type</i>	
Community cancer	Referent
Academic/research	0.61 (0.16–2.37)
Comprehensive community cancer	1.11 (0.27–4.50)
Other	— [†]
<i>Facility region</i>	
Eastern	Referent
Midwest	1.14 (0.35–3.72)
South	1.01 (0.43–2.34)
West	1.36 (0.48–3.87)
<i>Facility location</i>	
Metropolitan	Referent
Urban	1.01 (0.25–4.04)

	aHR
Rural	— [≠]
Unknown	0.80 (0.13–4.75)
<i>Year of diagnosis</i>	
1998	Referent
1999	0.41 (0.05–3.59)
2000	0.71 (0.09–5.76)
2001	0.68 (0.11–4.20)
2002	0.48 (0.09–2.62)
2003	0.50 (0.08–3.03)
2004	0.42 (0.06–2.83)
2005	0.66 (0.12–3.59)
2006	0.61 (0.11–3.37)
2007	0.88 (0.18–4.33)
2008	0.50 (0.06–3.90)
2009	0.82 (0.10–6.78)
2010	0.44 (0.10–1.98)
2011	0.45 (0.04–4.75)
2012	— [≠]
<i>Stage</i>	
IA	Referent
IB–IC	1.51 (0.43–5.28)
INOS	0.53 (0.03–8.72)
II	3.37 (1.12–10.17) *
III	8.26 (3.18–21.45) *
IV	29.49 (9.30–93.53) *
Unknown	6.31 (1.45–27.51) *
<i>Grade</i>	
Well	Referent
Moderate	0.65 (0.10–4.06)
Poorly	8.07 (2.13–30.61) *
Unknown	3.16 (0.76–13.13)
<i>Chemotherapy</i>	
No	Referent
Yes	0.55 (0.29–1.06)
Unknown	0.49 (0.05–5.17)

aHR: adjusted hazard ratio.

83 patients with missing vital status or follow-up time were excluded. Age, race, insurance status, income, facility type, region, location, year of diagnosis, stage, grade and chemotherapy were included in the marginal Cox proportional hazard model accounting for facility-level clustering.

—[≠] non-estimable.

* P<0.05.

Table 4

Five-year survival rates by stage and sub-stage

Five-year survival rate	
Stage	
I	98.3 (96.8–99.1)
IA	98.7 (96.7–99.4)
IB–IC	97.1 (91.0–99.1)
INOS	98.4 (89.4–99.8)
II	93.2 (82.8–97.4)
III	82.7 (74.3–88.5)
IV	72.0 (50.1–85.5)
Unknown	94.3 (85.4–97.8)

83 patients with missing vital status or follow-up time were excluded.