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Prognostic Value of Positive Peritoneal Lavage/Ascitic Cytology (FIGO Stage IC3) in Stage I Malignant Ovarian Germ Cell Tumors Treated with Reduced-Dose BEP Regimen

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Abstract

Objective This study aimed to evaluate the prognostic value of positive peritoneal lavage/ascitic cytology (FIGO stage IC3) in patients with stage I malignant ovarian germ cell tumors (MOGCT) treated with adjuvant reduced-dose bleomycin, etoposide, and cisplatin (BEP) chemotherapy.

Methods This multicenter retrospective cohort study included 112 MOGCT patients treated at three Chinese tertiary hospitals (2010-2024). All postoperative adjuvant chemotherapy used a uniform reduced-dose BEP regimen (bleomycin 15 mg/day, days 1-3). Stage I patients were divided into IC3 (positive cytology, n=7) and non-IC3 (negative cytology, n=87) groups. Kaplan-Meier curves and Cox proportional hazards models were used for survival and prognostic analyses.

Results After a median follow-up of 73 months, recurrence rates were 71.4% (5/7) in the IC3 group versus 3.4% (3/87) in the non-IC3 group (Log-rank P<0.0001). Positive peritoneal cytology was an independent adverse prognostic factor for recurrence (HR=32.23, 95% CI: 7.40-140.32, P<0.0001), adjusted for adjuvant chemotherapy. Notably, yolk sac tumor proportion was unexpectedly low in the IC3 group (14.3% vs 16.1% in non-IC3), suggesting the poor prognosis is driven by IC3 status itself rather than high-risk histology.

Conclusion Positive peritoneal lavage/ascitic cytology (FIGO stage IC3) is an independent high-risk marker for recurrence in stage I MOGCT. Given the small sample size and lack of standard-dose control, these findings are hypothesis-generating and require prospective validation.

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare ovarian malignancies, accounting for 2.6%-6.5% of ovarian cancers, predominantly affecting women aged 15–39 years [1–4]. Platinum-based chemotherapy, particularly the BEP regimen, has substantially improved outcomes, with 5-year overall survival exceeding 95% [2,5,6]. Fertility-sparing surgery (FSS) combined with platinum-based adjuvant chemotherapy is the standard of care for early-stage MOGCT, jointly recommended by NCCN and ESMO guidelines [5,7,8]. Multiple studies have confirmed FSS safety, with postoperative spontaneous pregnancy rates of 70%-80% [2,9,10].

Bleomycin has well-documented dose-dependent pulmonary toxicity, with risk increasing 3.5-fold at cumulative doses > 300–330 mg [11,12]. The incidence of bleomycin-induced pneumonitis ranges from 2% to 46%, related to total dose, age, and renal function [12]. To reduce pulmonary toxicity, many Chinese centers have adopted a reduced-dose BEP regimen, decreasing bleomycin from 90 mg to 45 mg per cycle. However, Satoh et al. [13] argued that standard-dose BEP is essential for ovarian yolk sac tumors, and dose reduction may compromise efficacy. Real-world evidence on reduced-dose BEP across MOGCT risk strata remains scarce [14].

The 2014 FIGO staging system classifies positive peritoneal lavage/ascitic cytology as stage IC3, still considered early-stage disease [15]. In contrast, the pediatric CCG/POG staging system equates positive ascitic cytology with peritoneal implantation, classifying it as stage III and recommending intensified chemotherapy [16]. Billmire et al. [16] confirmed that positive ascitic cytology is an adverse prognostic indicator warranting stage upgrade. However, pediatric and adult MOGCT differ substantially in pathological type distribution (children: immature teratoma; adults: dysgerminoma and yolk sac tumor) and biological behavior. The independent prognostic value of IC3 in adults has not been systematically validated [17,18].

This multicenter retrospective cohort study was therefore conducted to evaluate the independent prognostic value of positive peritoneal lavage/ascitic cytology (FIGO stage IC3) in patients treated with reduced-dose BEP, providing evidence for refined risk stratification of early-stage MOGCT.

Materials and Methods

Study Design and Patients

This multicenter retrospective cohort study consecutively included 112 pathologically confirmed MOGCT patients treated at Beijing Obstetrics and Gynecology Hospital, Capital Medical University; Beijing Tongren Hospital; and Shunyi Maternal and Children's Hospital of Beijing Children's Hospital, Capital Medical University, from January 2010 to April 2024.

Inclusion criteria: (1) postoperative pathological diagnosis of MOGCT; (2) initial fertility-sparing surgery or comprehensive staging laparotomy [19,20]; (3) uniform reduced-dose BEP adjuvant chemotherapy; (4) complete clinicopathological, treatment, and follow-up data; (5) pathological typing and staging per 2020 WHO Classification and 2014 FIGO system [15].

Exclusion criteria: (1) synchronous or previous other malignancies; (2) neoadjuvant chemotherapy or radiotherapy [21]; (3) non-BEP regimen or incomplete bleomycin records; (4) follow-up <6 months without endpoint events.

Definitions

FIGO stage IC3: Positive malignant cells in intraoperative peritoneal lavage or ascites per 2014 FIGO criteria. Non-IC3 group: FIGO stages IA, IB, IC1, IC2 with negative cytology.

Reduced-dose BEP: Bleomycin 15 mg/day (days 1-3); etoposide 100 mg/m²/day (days 1-5); cisplatin 20 mg/m²/day (days 1-5); 21-day cycles.

Outcomes

Primary endpoint: Recurrence-free survival (RFS)—time from surgery to imaging/pathological confirmation of recurrence or all-cause death.

Secondary endpoints: Overall survival (OS), subgroup recurrence rates.

Statistical Analysis

Continuous variables were compared using t-test or Wilcoxon rank-sum test; categorical variables using χ^2 or Fisher's exact test. RFS curves were plotted via Kaplan-Meier with Log-rank tests.

Given only 8 recurrence events, multivariate Cox regression included only univariate significant variables ($P<0.05$) plus adjuvant chemotherapy adjustment. The final model had 2 covariates, with events per variable (EPV)=4—below ideal threshold but the most parsimonious model supported by the data. Model discrimination was assessed by C-index. No formal multiple comparison correction was performed for the 9-variable univariate analysis; if Bonferroni correction ($\alpha=0.0056$) were applied, IC3 would remain significant while family history would be borderline. All tests were two-sided, $P<0.05$ considered significant. Analyses used R 4.3.0.

Results

Baseline Characteristics

Of 112 MOGCT patients, 94 (83.9%) had FIGO stage I disease (IC3: n=7; non-IC3: n=87); 18 had stage II-IV. IC3 group median age was 26 years (range 13-30), non-IC3 24 years (12-45) ($P>0.999$). Chemotherapy rates were 57.1% (4/7) in IC3 versus 64.4% (56/87) in non-IC3 ($P=0.701$). Notably, yolk sac tumor proportion was 14.3% (1/7) in IC3 versus 16.1% (14/87) in non-IC3 ($P>0.999$). Tumor >10 cm: 42.9% vs 63.2% ($P=0.422$). Fertility-sparing surgery: 100% vs 97.7% ($P>0.999$) (Table 1).

Table 1. Baseline characteristics (FIGO stage I, n=94)

Variable	IC3 (n=7)	Non-IC3 (n=87)	P
Median age (range), years	26 (13-30)	24 (12-45)	>0.999
Yolk sac tumor, n (%)	1 (14.3)	14 (16.1)	>0.999
Tumor >10 cm, n (%)	3 (42.9)	55 (63.2)	0.422
Adjuvant chemo, n (%)	4 (57.1)	56 (64.4)	0.701
FSS, n (%)	7 (100)	85 (97.7)	>0.999

Note: Wilcoxon rank-sum test for age; Fisher's exact test for categorical variables.

Univariate Cox regression of 9 clinicopathological variables showed only tumor family history (HR=10.10, 95% CI: 2.01-50.20, P=0.005) and positive peritoneal cytology (HR=16.80, 95% CI: 4.00-70.50, P<0.0001) significantly associated with recurrence (Table 2). In a separate univariate model with IC3 alone, HR=30.26 (95% CI: 7.13-128.38, P<0.0001). As shown in Figure 2, the forest plot visualizes this univariate Cox regression result for IC3 versus non-IC3.

Recurrence Outcomes

Median follow-up: 73 months (range 6-176). Overall, 8 patients (7.1%) recurred and 1 (0.9%) died; all recurrences occurred in stage I patients. Recurrence rate: 71.4% (5/7) in IC3 vs 3.4% (3/87) in non-IC3 (Log-rank P<0.0001) (Figure 1). Among IC3 patients, 2/4 receiving reduced-dose BEP recurred, while all 3 untreated patients recurred. In non-IC3, recurrence was 1.8% (1/56) with chemotherapy versus 6.5% (2/31) without. None of the 18 stage II-IV patients recurred—a descriptive observation limited by small sample size and selection bias, not suitable for direct comparison with IC3.

Multivariate Analysis

Given only 8 events, multivariate Cox regression included positive peritoneal cytology and adjuvant chemotherapy only (Table 3). Family history was excluded to avoid overfitting (EPV=2.7 if included). After adjustment, positive peritoneal cytology remained an independent risk factor (HR=32.23, 95% CI: 7.40-140.32, P<0.0001); adjuvant chemotherapy showed a weak protective trend (HR=0.30, 95% CI: 0.07-1.30, P=0.107). Model C-index=0.84. The wide confidence interval reflects estimate instability; findings are exploratory.

Table 2. Univariate Cox regression (n=112)

Variable	HR (95% CI)	P
Age	0.94 (0.85-1.04)	0.225
Family history	10.10 (2.01-50.20)	0.005*
Positive peritoneal cytology	16.80 (4.00-70.50)	<0.001*
Tumor laterality	1.11 (0.14-9.07)	0.922
FIGO stage (II-IV vs I)	0.56 (0.10-2.86)	0.351
Adjuvant chemo (yes vs no)	0.25 (0.06-1.04)	0.056
Tumor diameter	1.06 (0.97-1.16)	0.183
Surgical method	1.34 (0.27-6.64)	0.723
Pathological type	0.86 (0.46-1.59)	0.627

Table 3. Multivariate Cox regression (stage I, n=94)

Variable	HR (95% CI)	P
IC3 vs negative	32.23 (7.40-140.32)	<0.0001
Adjuvant chemo (yes vs no)	0.30 (0.07-1.30)	0.107

Model C-index=0.84; EPV=4.

Discussion

This multicenter retrospective cohort study confirms that positive peritoneal lavage/ascitic cytology (FIGO stage IC3) is an independent high-risk prognostic indicator in stage I MOGCT. Most prior MOGCT prognostic studies have focused on pathological type, tumor markers, and overall FIGO stage, rarely analyzing peritoneal cytology separately [17,22–24]. Murugaesu et al. [22] and Kawai et al. [25] did not include ascitic cytology as an independent variable. To our knowledge, this is the first study to quantify IC3-associated recurrence risk in a Chinese population treated with reduced-dose BEP.

The IC3 subgroup recurrence rate of 71.4% was > 20-fold higher than that of non-IC3 stage I patients (3.4%), with a ~ 30-fold increased risk after adjustment. Notably, the IC3 group had a yolk sac tumor proportion of only 14.3%—lower than the non-IC3 group (16.1%). This unexpected finding has important biological implications: the poor prognosis of IC3 is not simply driven by high-risk histology, but more likely reflects the peritoneal dissemination capacity conferred by positive cytology itself. Even for common non-yolk sac subtypes (dysgerminoma, immature teratoma), positive ascitic cytology appears to “upgrade” clinical behavior. This observation supports IC3 status as a high-risk marker independent of histological subtype. Positive peritoneal cytology is a known adverse factor in epithelial ovarian cancer [26], but its value in germ cell tumors has been underappreciated.

The core clinical dilemma concerns dosage. None of the 18 stage II-IV patients receiving reduced-dose BEP recurred, seemingly contradicting the high recurrence in IC3. However, this reflects baseline incomparability—substantial differences in tumor burden, pathological composition (stage II-IV may contain more chemosensitive dysgerminoma), and surgical extent—and the stage II-IV group had only 18 patients, making the zero-recurrence result potentially a small-sample coincidence. Thus, this study can neither prove reduced-dose BEP is “insufficient” for IC3 nor exclude dose-related effects, as no standard-dose control group exists. The high recurrence risk of IC3 may result from an interaction between intrinsic tumor aggressiveness and insufficient chemotherapy exposure, requiring future prospective studies with standard-dose controls.

The discordance between 2014 FIGO and CCG/POG staging systems regarding ascitic cytology [16] is echoed here: classifying IC3 as stage I may underestimate its risk. Although our sample size is insufficient to prompt staging revision, we strongly suggest clinicians regard IC3 as a “high-risk sentinel subgroup” within stage I, with enhanced postoperative imaging and tumor marker surveillance.

Tamauchi et al. [10] and Ayhan et al. [8] emphasized that precise risk stratification is essential for balancing fertility preservation and oncologic safety—IC3 may be a key consideration.

Future molecular studies [31,32] could explore the genomic drivers of IC3's high dissemination potential through microdissection or liquid biopsy, potentially identifying new therapeutic targets.

Limitations

Small sample and unstable estimates

The IC3 subgroup included only 7 patients, with 8 total recurrence events. EPV = 4, far below ideal, resulting in an extremely wide 95% CI (7.40-140.32) and risk of overestimation. Findings are hypothesis-generating and require external validation.

Retrospective selection bias and unmeasured confounding

Three untreated IC3 patients had clear indication confounding. Potential confounders (baseline AFP/LDH, chemotherapy timing) were missing due to inconsistent center records.

No standard-dose control

The entire cohort received reduced-dose BEP only, precluding direct dose comparison.

No histological subtype stratification

Subtype-specific analysis was precluded by tiny sample sizes after further stratification within IC3.

Conclusion

Positive peritoneal lavage/ascitic cytology (FIGO stage IC3) is an independent high-risk prognostic marker for recurrence in stage I MOGCT, independent of reduced-dose BEP adjuvant chemotherapy. The current FIGO stage I system fails to distinguish this subgroup's exceptionally high recurrence risk. Given the inherent methodological limitations—extremely small sample size and lack of standard-dose control—we cannot distinguish the respective contributions of intrinsic tumor aggressiveness versus insufficient chemotherapy dose. Therefore, blind chemotherapy intensification is not recommended based on these data. Clinically, enhanced follow-up monitoring for IC3 patients is advised. Prospective controlled studies with standard-dose comparators are urgently needed to validate IC3's prognostic value and define optimal treatment for this high-risk population.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (approval number: 2025-KY-053-01). All procedures were performed in

accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable. No individual person's data (e.g., images or videos) are presented in this manuscript.

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Author contributions

Huiyi Tan: Conceptualization, Data curation, Formal analysis, Writing – original draft, Visualization.

Yumei Wu (Corresponding author/Supervisor): Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Writing – review & editing.

Ming Wang: Writing – review & editing, Validation.

Yu Cai: Data curation, Investigation, Validation.

All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to the respective institutional policies of the participating hospitals.

Competing interests

The authors declare that they have no competing interests.

References

1. Hubbard A K, Poynter J N. Global incidence comparisons and trends in ovarian germ cell tumors by geographic region in girls, adolescents and young women: 1988-2012. Gynecol Oncol, 2019, 154(3): 608-615.
2. Pauniaho S L, Salonen J, Helminen M, et al. The incidences of malignant gonadal and extragonadal germ cell tumors in males and females: a population-based study covering over 40 years in Finland. Cancer Causes Control, 2012, 23(12): 1921-1927.
3. Morrison A, Nasioudis D. Reproductive outcomes following fertility-sparing surgery for malignant ovarian germ cell tumors: a systematic review of the literature. Gynecol Oncol, 2020, 158(2): 476-483.

4. [illegible] Meta [illegible]2021, 37(2): 198-202.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version X.2024. Fort Washington: NCCN, 2024.
6. Williams S, Blessing J A, Liao S Y, et al. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the gynecologic oncology group. J Clin Oncol, 1994, 12(4): 701-706.
7. [illegible]2006, 41(4): 256-259.
8. Ayhan A, Tunç M, Akıllı H, et al. Fertility-sparing approach to malignant ovarian germ cell tumors — Oncologic and obstetric outcome: A retrospective study. Int J Gynaecol Obstet, 2024, 164(3): 1074-1079.
9. Weinberg L E, Lurain J R, Singh D K, et al. Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumors. Gynecol Oncol, 2011, 121(2): 285-289.
10. Tamauchi S, Kajiyama H, Yoshihara M, et al. Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicenter study. Am J Obstet Gynecol, 2018, 219(4): 385.e1-385.e7.
11. O'Sullivan J M, Huddart R A, Norman A R, et al. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol, 2003, 14(1): 91-96.
12. Sleijfer S. Bleomycin-induced pneumonitis. Chest, 2001, 120(2): 617-624.
13. Satoh T, Aoki Y, Kasamatsu T, et al. Administration of standard-dose BEP regimen is essential for treatment of ovarian yolk sac tumour. Eur J Cancer, 2015, 51(3): 340-351.
14. [illegible]. BEP [illegible]2022, 32(5): 456-461.
15. WHO Classification of Tumours Editorial Board. WHO classification of tumours: female genital tumours. 5th ed. Lyon: IARC Press, 2020.
16. Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg, 2004, 39(3): 424-429.
17. de La Motte Rouge T, Pautier P, Rey A, et al. Prognostic factors in women treated for ovarian yolk sac tumour: a retrospective analysis of 84 cases. Eur J Cancer, 2011, 47(2): 175-182.
18. Tong X, You Q, Li L, et al. Prognostic factors of patients with ovarian yolk sac tumors: a study in Chinese patients. Onkologie, 2008, 31(12): 679-684.
19. Ertas I E, Taskin S, Goklu R, et al. Long-term oncological and reproductive outcomes of fertility-sparing cytoreductive surgery in females aged 25 years and younger. J Obstet Gynaecol Res, 2014, 40(3): 797-805.
20. Zhang G Y, Zhang R, Wu L Y, et al. Neoadjuvant BEP chemotherapy in extensively advanced yolk sac tumors. Int J Gynecol Cancer, 2018, 28(4): 713-720.
21. Murugaesu N, Schmid P, Dancey G, et al. Malignant ovarian germ cell tumors: identification of novel prognostic markers. J Clin Oncol, 2006, 24(30): 4862-4866.

22. Nawa A, Obata N, Kikkawa F, et al. Prognostic factors of patients with yolk sac tumors of the ovary. Am J Obstet Gynecol, 2001, 184(6): 1182-1188.
23. de la Motte Rouge T, Pautier P, Genestie C, et al. Early AFP decline as prognostic marker for ovarian yolk sac tumors. Gynecol Oncol, 2016, 142(3): 452-457.
24. Kawai M, Kano T, Furuhashi Y, et al. Prognostic factors in yolk sac tumors of the ovary. Cancer, 1991, 67(1): 184-192.
25. Krugmann J, Lang Schwarz C, Melcher B, et al. Malignant ascites in high-grade serous ovarian carcinoma. Arch Gynecol Obstet, 2019, 299(2): 515-523.
26. Gershenson D M, Miller A M, Champion V L, et al. Long-term reproductive outcomes after platinum chemotherapy for ovarian germ cell tumors. J Clin Oncol, 2007, 25(19): 2792-2797.
27. Chu R, Liu P, Chen J, et al. BEP vs TC regimen in fertility-sparing MOGCT treatment. J Gynecol Oncol, 2023, 34(2): e12.
28. de La Motte Rouge T, Pautier P, Duvillard P, et al. Survival outcomes of ovarian yolk sac treated with BEP. Ann Oncol, 2008, 19(8): 1435-1441.
29. Gershenson D M, Copeland L J, Kavanagh J J, et al. VAC regimen for non-dysgerminomatous germ cell tumors. Cancer, 1985, 56(12): 2756-2761.
30. Kraggerud S M, Hoei-Hansen C E, Alagaratnam S, et al. Molecular features of ovarian germ cell tumors. Endocr Rev, 2013, 34(3): 339-376.
31. Van Nieuwenhuysen E, Busschaert P, Neven P, et al. Genomic landscape of ovarian germ cell tumors. Gynecol Oncol, 2018, 151(1): 61-68.
32. Berney D M, Stoneham S, Arora R, et al. Histopathological classification of ovarian germ cell tumours. Histopathology, 2020, 76(1): 25-36.

Figures

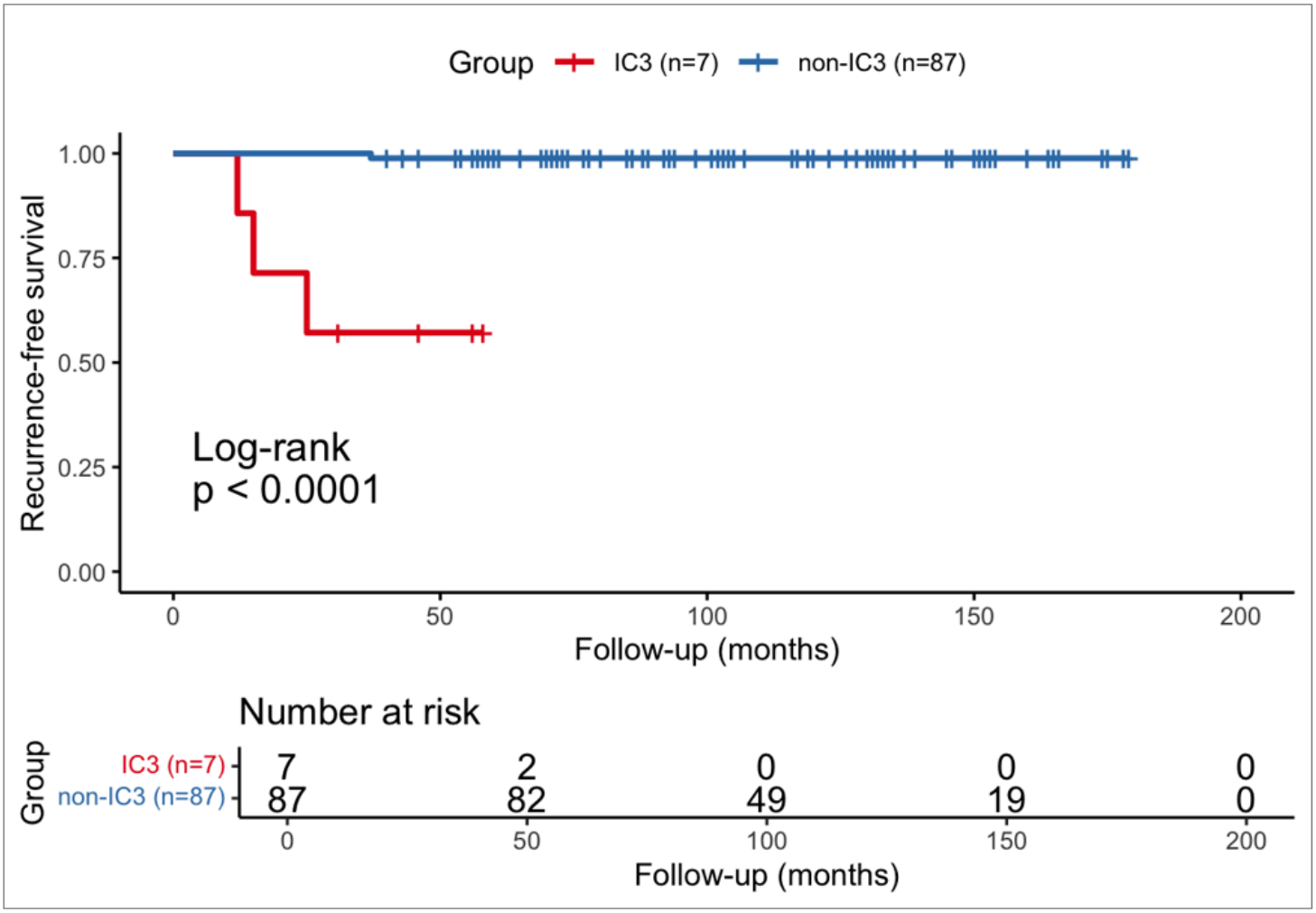


Figure 1

Kaplan-Meier RFS curves (IC3 vs non-IC3). Red: IC3 (n=7); blue: non-IC3 (n=87). Log-rank P<0.0001.

Figure note: The red curve represents the IC3 group (n=7), and the blue curve represents the non-IC3 group (n=87); the risk number table at each follow-up node is shown below the figure, Log-rank test P<0.0001; the survival curve of the IC3 group drops significantly in the early follow-up period, and the recurrence-free survival is significantly inferior to that of the non-IC3 group.

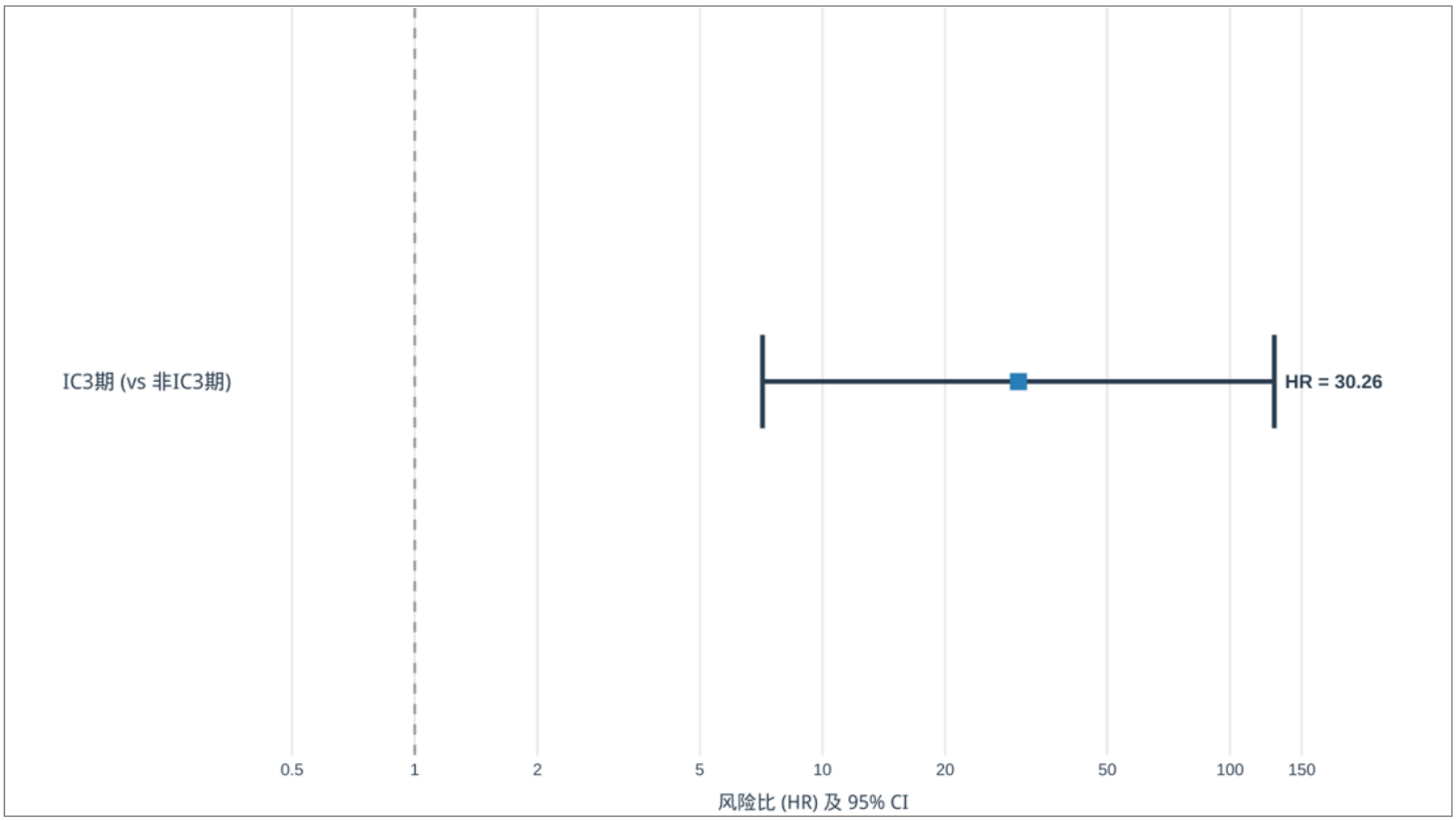


Figure 2

Forest plot: IC3 univariate Cox regression. HR=30.26(95%CI:7.13-128.38),P<0.0001.

Figure note: The square represents the recurrence risk ratio HR=30.26 of IC3 stage compared with non-IC3 stage, and the horizontal line represents the 95% confidence interval (7.13–128.38); the vertical dashed line is the invalid reference line of HR=1, the X-axis is on a logarithmic scale, and P<0.0001.