Low-grade serous ovarian cancer in Indonesia: Insights from the largest multicenter cohort in a middle-income country

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Abstract. Low-grade serous ovarian cancer (LGSOC), a rare subtype of epithelial ovarian cancer, is characterized by indolent growth and limited chemosensitivity. However, data from low- and middle-income countries are limited. The present study aimed to describe the clinical and pathological characteristics of patients with LGSOC in Indonesia. This retrospective multicenter study was conducted at nine tertiary cancer centers across seven provinces, and included patients with histologically confirmed LGSOC diagnosed according to the 2020 World Health Organization Classification of Female Genital Tumors between January 2019 and December 2024. Demographic, clinical, surgical, pathological and treatment data were extracted from medical records. Recurrence was classified as early (<6 months) or late (≥6 months) after completion of primary treatment. Associations between clinicopathological variables and outcomes were analyzed using Fisher's exact test. Kaplan-Meier (KM) survival analysis with log-rank testing and Cox proportional hazards regression were performed, with a restricted multivariate model to minimize overfitting due to limited events. A total of 160 patients (median age, 46 years; range, 17-75 years) were included, with a median follow-up of 24 months. Of the cohort, ~50% presented with advanced-stage disease (International Federation of Gynecology and Obstetrics III-IV, 50%). Ascites and elevated cancer antigen-125 levels were observed in 43.1 and 70.6% of patients, respectively. Primary debulking surgery was performed in 90% of cases, achieving optimal cytoreduction in 72.5%. The overall recurrence rate was 10, and 92.5% of patients were alive at the last follow-up. KM analysis showed worse survival in patients with advanced-stage disease and residual disease. In univariate Cox regression, residual disease (HR, 7.93) and recurrence (HR, 10.06) showed the strongest associations with mortality. In multivariate analysis, only residual disease remained an independent predictor (adjusted HR, 5.59; P=0.013). In this multicenter cohort, residual disease was the key determinant of survival, underscoring the importance of complete cytoreductive surgery and early diagnosis.

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Abbreviations: CA-125, cancer antigen-125; FIGO, International Federation of Gynecology and Obstetrics; LGSOC, low-grade serous ovarian cancer

Key words: LGSOC, multicenter study, prognostic factors, cytoreductive surgery, Indonesia

Introduction

Low-grade serous ovarian cancer (LGSOC) is a rare, distinct subtype of epithelial ovarian cancer, accounting for 2-5%

of all epithelial ovarian malignancies and 4-5% of serous tumors globally (1-3). LGSOC predominantly affects women at a slightly younger median age than that associated with high-grade serous ovarian cancer, with median ages at diagnosis being 54-56 years globally, compared with ~62 years in high-grade disease (3-6).

LGSOC is characterized by indolent clinical behavior, slow progression and markedly prolonged survival times compared with high-grade serous ovarian cancer, as well as minimal responsiveness to conventional cytotoxic chemotherapy (1,5,6). The hallmark histopathological features of LGSOC include mild-to-moderate nuclear atypia and low mitotic activity (<12 mitoses per 10 high-power fields). These diagnostic criteria are consistent with the 2020 World Health Organization (WHO) Classification of Female Genital Tumors (7). Microscopically, LGSOC often shows cuboidal or columnar cells with amphophilic cytoplasm and frequent psammoma bodies, and is associated with borderline serous tumors, supporting the hypothesis of a stepwise progression from benign or borderline lesions (1,2).

Despite the slower progression and distinct tumor biology compared with high-grade serous ovarian cancer, LGSOC often presents at advanced stages, and optimal cytoreductive surgery remains the cornerstone of initial treatment because the volume of residual disease is the most meaningful predictor of survival (1,2,5). Platinum-based chemotherapy is the standard adjuvant therapy but shows limited efficacy; therefore, hormonal maintenance therapy and targeted agents are increasingly used (8). Epidemiological data from Indonesia mirror global patterns, with the majority of patients with LGSOC presenting in their mid-50s, similar to trends observed in international cohorts (3-6), and a high proportion of diagnoses at advanced International Federation of Gynecology and Obstetrics (FIGO) stages (9). Survival outcomes are heavily influenced by the stage at diagnosis and surgical success, highlighting the universal need for improved early detection, refined surgical strategies and expanded access to innovative therapies (1,2,9).

Given the rarity of LGSOC, conducting robust clinical research and accumulating sufficient patient data through single-center studies presents substantial challenges. The limited patient population and geographical dispersion necessitate collaborative efforts to gain meaningful insights into the natural history, molecular characteristics and optimal treatment approaches of the disease. Therefore, multicenter studies involving multiple institutions and research groups are key to overcoming the limitations of small sample sizes inherent to rare types of cancer. Moreover, this approach allows for comprehensive analyses of clinical outcomes, identification of prognostic factors and the development of novel therapies (4). This collaborative paradigm is essential for advancing the understanding of LGSOC and ultimately improving patient care for this challenging disease.

To date, a comprehensive LGSOC profile has not been established in Indonesia. In low- and middle-income countries (LMICs), challenges such as delayed referral from primary care facilities, unequal access to advanced imaging, variability in surgical expertise and the absence of robust national cancer registries may substantially influence stage at diagnosis and treatment outcomes. Consequently, real-world data from LMIC settings are essential to understand how systemic healthcare factors interact with tumor biology and surgical management in shaping patient prognosis. To the best of our knowledge, the present study represents the first multicenter analysis of LGSOC in Indonesia and includes one of the largest cohorts reported in an LMIC setting. The present study aimed to characterize the clinicopathological features, surgical outcomes and recurrence patterns in this cohort within a diverse national referral network.

Materials and methods

Study design and patient population. The present study encompassed nine tertiary cancer centers [Dr. Soetomo General Academic Hospital and Universitas Airlangga Hospital (Surabaya, Indonesia), Dr. Kariadi General Hospital (Semarang, Indonesia), Dr. Cipto Mangunkusumo Hospital and Gatot Soebroto Army Central Hospital (Jakarta, Indonesia), Ngoerah General Hospital (Denpasar, Indonesia), Dr. Hasan Sadikin General Hospital (Bandung, Indonesia), Ulin General Hospital (Banjarmasin, Indonesia), Dr. Wahidin Sudirohusodo General Hospital (Makassar, Indonesia)] located across seven provinces of Indonesia (East Java, Central Java, West Java, Jakarta, Bali, South Kalimantan, and South Sulawesi), representing major referral hubs that collectively capture patients from diverse ethnic and geographic backgrounds. This multicenter retrospective study used a total sampling approach across nine referral hospitals in Indonesia. All patients diagnosed with and undergoing surgery for LGSOC between January 2019 and December 2024 were identified and included without age restriction. The observed patient age range was 17-75 years. Inclusion criteria comprised: I) Histopathologically confirmed LGSOC based on the 2020 WHO Classification of Female Genital Tumors, characterized by low-grade nuclear atypia and low mitotic activity; and ii) availability of clinical and surgical records. Patients with incomplete data regarding the primary diagnosis, FIGO stage, or surgical outcomes were excluded from the analysis (7). The presence of residual disease after surgery was recorded as a binary variable: Optimal cytoreduction (no visible residual disease) or suboptimal cytoreduction (any visible residual disease). This binary classification was used consistently throughout the study.

Data collection. Data were extracted from the patients' medical records, and the following variables were collected: i) Demographic data: Age at diagnosis, parity (nulliparous, primiparous, multiparous) and BMI; ii) clinical characteristics: FIGO stage, presence of comorbidities (hypertension and diabetes mellitus) and presence of ascites at surgery; iii) treatment and pathological data: Primary treatment modality (primary debulking surgery or neoadjuvant chemotherapy), largest tumor diameter (cm), presence of residual disease after surgery (optimal, no visible disease; suboptimal, visible disease) and administration of adjuvant chemotherapy; and iv) outcome data: Presence of disease recurrence and patient condition at the last follow-up (alive without disease, alive with disease or succumbed to disease).

Owing to heterogeneity in electronic medical record systems across participating centers, certain variables (including BMI, CA-125 levels and tumor size) were

incompletely documented. No data imputation methods were applied. For each statistical comparison, analyses were conducted using available data; patients with missing data for a given variable were excluded only from that specific analysis. Molecular profiling data (such as KRAS, BRAF, NRAS mutations and hormone receptor status) were not routinely available in this retrospective dataset and were, therefore, not analyzed.

Follow-up and outcome definition. Follow-up evaluations were conducted at ~6-month intervals; however, specific schedules and imaging modalities were not fully standardized across centers. Recurrence was defined as clinical, radiological or biochemical evidence of disease after completion of primary treatment. Radiological recurrence was based on imaging findings (ultrasound, CT or MRI), whereas biochemical recurrence was considered when CA-125 elevation was accompanied by clinical suspicion or imaging confirmation. The timing of recurrence was calculated from the completion of primary treatment.

Statistical analysis. Descriptive statistics were used to summarize the data collected. Continuous variables (age and tumor size) are presented as a median value and range, and categorical variables are presented as a frequency and percentage. Fisher's exact test was used to evaluate associations between categorical variables because several subgroup sample sizes were small. Kaplan-Meier (KM) survival analysis with log-rank testing was performed to evaluate differences in overall survival (OS) across subgroups. Cox proportional hazards regression was conducted to estimate HRs, including univariate analyses for all clinically relevant variables and a restricted multivariate model incorporating a limited number of key covariates selected *a priori* to minimize overfitting. Analyses were performed in R (version 4.4.1; R Foundation for Statistical Computing). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient demographic and clinicopathological characteristics. A total of 160 patients met the inclusion criteria. The demographic and clinical characteristics of the patients are summarized in Table I. The median age at diagnosis was 46 years (range, 17-75 years). The majority of patients were multiparous (43.8%). Of all patients, half (50%) presented with advanced-stage disease (stage III or IV). The median tumor size was 14 cm (range, 2-40 cm) and 69 patients (43.1%) had ascites at the time of surgery. BMI, tumor size and cancer antigen-125 (CA-125) level data were incomplete in some cases owing to differences in hospital medical record formats and inconsistent documentation. Analyses involving these variables were thus conducted using available case analysis, and denominators varied accordingly across specific comparisons.

Recurrence patterns and survival outcomes. Of the patients with advanced stages of ovarian cancer (III and IV), 72 (90%) underwent primary debulking surgery and 8 (10%) underwent neoadjuvant chemotherapy (Table II). Patients who received neoadjuvant chemotherapy were included in the overall surgical outcome analysis based on residual disease status following

Table I. Baseline demographic and clinical characteristics.

Characteristic	Value
Median age, years (min.-max.)	45.5 (17-75)
Parity, n (%)	
Nulliparous	62 (38.8)
Primiparous	28 (17.5)
Multiparous	70 (43.8)
BMI, n (%)	
Underweight	17 (10.6)
Normal	53 (33.1)
Overweight	25 (15.6)
Obese	50 (31.3)
Missing	15 (9.4)
CA-125 level, n (%)	
Normal	4 (2.5)
Abnormal	113 (70.6)
Missing	43 (26.9)
FIGO stage, n (%)	
I	58 (36.3)
II	22 (13.7)
III	71 (44.4)
IV	9 (5.6)
Ascites, n (%)	
Present	69 (43.1)
Absent	91 (56.9)
Tumor size	
Median, cm (min.-max.)	14 (2-40)
Missing, n (%)	17 (10.6)
Metastasis, n (%)	
Omentum	
Yes	38 (23.8)
No	122 (76.3)
Lymph gland	
Yes	13 (8.1)
No	147 (91.9)
Comorbidity, n (%)	
Hypertension	
Yes	25 (15.6)
No	135 (84.4)
Diabetes mellitus	
Yes	9 (5.6)
No	151 (94.4)
Pelvic lymph node dissection, n (%)	
Yes	38 (23.7)
No	122 (76.3)
Para-aortic lymph node dissection, n (%)	
Yes	17 (10.6)
No	143 (89.4)

FIGO, International Federation of Gynecology and Obstetrics; CA-125, cancer antigen-125.

interval debulking surgery. Of all patients with advanced-stage disease, 72.5% underwent optimal cytoreduction (no visible residual disease) and 27.5% underwent suboptimal cytoreduction (with visible residual disease). A detailed categorization (<1 cm vs. ≥1 cm) was not possible because of documentation limitations. After surgery, 119 patients (74.4%) received adjuvant chemotherapy. Follow-up evaluations for recurrence were generally conducted at ~6-month intervals; however, the actual timing and methods varied across centers. Disease recurrence was identified based on clinical assessment supported by imaging modalities such as ultrasound, CT or MRI when indicated by symptoms or rising CA-125 levels.

A total of 16 patients (10%) experienced disease recurrence. Recurrence events included radiological and clinically confirmed cases; isolated biochemical elevation without supportive clinical or imaging findings was not classified as recurrence. During the final assessment in June 2025, with a median follow-up duration of 24 months, the estimated OS rates were 100% at 1 year, 95.6% (95% CI, 92.2-99.1) at 2 years, 89.9% (95% CI, 83.8-96.4) at 3 years and 84.9% (95% CI, 76.4-94.4) at 5 years. A total of 148 patients (92.5%) were alive and 12 patients (7.5%) had succumbed (Table II). The median OS was not reached during the follow-up period. Given the indolent biology of LGSOC, this follow-up duration may underestimate long-term recurrence and survival events. Analysis of prognostic factors showed that the presence of a residual tumor after surgery was the most substantial predictor of subsequent recurrence. Among the patients, 31.8% (7/22) with residual disease experienced recurrence compared with 6.5% (9/138) without residual disease (Table III).

Association between residual disease and recurrence risk. In this cohort, the overall recurrence rate was 10.0% (95% CI, 5.4-14.7). Patients with residual tumors after surgery had a markedly higher recurrence rate [31.8% (95% CI, 12.4-51.3%)] when compared with those who achieved complete debulking [6.5% (95% CI, 2.4-10.6%)]. The absolute risk difference was 25.3% (95% CI, 5.5-45.1%), corresponding to a ~5-fold increase in relative risk (4.88; 95% CI, 2.03-11.75). This association was statistically significant, underscoring the prognostic importance of achieving no residual disease at the time of primary surgery. The key prognostic associations are summarized in Table III.

Prognostic factors associated with surgical and survival outcomes. Analysis of prognostic factors showed that the presence of a residual tumor after surgery was the most substantial predictor of subsequent recurrence (P<0.001). Furthermore, the cancer stage at diagnosis was a major factor in determining surgical success. Patients with advanced-stage disease (stage III/IV) were significantly more likely to undergo suboptimal cytoreduction than those with early-stage disease (P<0.001; Table III). Consistent with these findings, the stage at diagnosis was significantly associated with the disease status of patients at last follow-up (P=0.004; Table III), with higher stages being associated with worse survival outcomes. However, no statistically significant association was found between cancer stage and primary tumor size in this cohort (P=0.128). All reported associations represent the results of unadjusted analyses.

Table II. Treatment and patient outcomes.

Characteristic	Value
Primary treatment, n (%)	
Primary debulking surgery	72 (90.0)
FIGO stage	
III	66 (91.7)
IV	6 (8.3)
Neoadjuvant chemotherapy	8 (10.0)
FIGO stage	
III	5 (62.5)
IV	3 (37.5)
Residual disease, n (%)	
Yes	22 (27.5)
No (complete debulking)	58 (72.5)
Optimal cytoreduction, n (%)	
Stage III	51 (88.0)
Stage IV	7 (12.0)
Adjuvant chemotherapy, n (%)	
Yes	119 (74.4)
Paclitaxel-carboplatin	113 (70.6)
Others	6 (3.8)
No	41 (25.6)
Median follow-up period, years (min.-max.)	2 (1-6)
Recurrence, n (%)	
Yes	16 (10.0)
≥6 months	10 (6.2)
<6 months	6 (3.8)
No	144 (90.0)
Current condition, n (%)	
Alive	148 (92.5)
Deceased	12 (7.5)

FIGO, International Federation of Gynecology and Obstetrics.

Kaplan-Meier analysis of overall survival according to baseline characteristics. KM curves for OS are shown in Fig. 1. The median OS was not reached (Fig. 1A). No significant differences in survival were observed across age groups (log-rank P=0.267; Fig. 1B), parity (log-rank P=0.817; Fig. 1C) or BMI categories (log-rank P=0.508; Fig. 1D), with largely overlapping survival curves. Preoperative CA-125 levels were also not associated with OS (log-rank P=0.841; Fig. 1E), although interpretation is limited by a high proportion of missing data (26.9%). These findings suggest that baseline demographic and selected clinical characteristics did not significantly influence OS in this cohort.

Kaplan-Meier analysis of overall survival according to clinicopathological and treatment factors. KM analyses of OS according to clinicopathological and treatment-related factors are presented in Fig. 2. Patients with advanced-stage disease (FIGO stages III-IV) demonstrated significantly worse OS compared with those with early stage disease (stages I-II)

Table III. Association of clinical factors with outcomes.

Association tested	Patient distribution	Statistical result	Effect estimate	Key finding
Stage vs. residual disease	Residual disease present: 22 patients; no. residual disease: 138 patients	P<0.001	-	Advanced stage was significantly associated with suboptimal debulking
Residual disease vs. recurrence	Recurrence in residual disease group: 7/22 (31.8%); recurrence in no residual disease group: 9/138 (6.5%)	P<0.001	Absolute risk difference: 25.3% (95% CI, 5.5-45.1%); relative risk: 4.88 (95% CI, 2.03-11.75)	Residual disease was significantly associated with increased recurrence risk
Stage vs. tumor size	Higher stage group vs. lower stage group	P=0.128	-	Higher stage was not significantly associated with larger tumor size
Stage vs. current condition	Worse condition observed more frequently in advanced-stage patients	P=0.004	-	Higher stage was associated with worse clinical condition

The overall recurrence rate in the cohort was 10% (16/160; 95% CI, 5.4-14.7%). Fisher's exact test was used to evaluate the association between residual disease and recurrence. CI, confidence interval.

(log-rank P=0.025; Fig. 2A). Similarly, the presence of omental metastasis (P=0.011), peritoneal carcinomatosis (P<0.001), ascites (P=0.005), residual disease after surgery (P<0.001) and recurrence (P<0.001) were all significantly associated with worse survival outcomes (Fig. 2C-E, H and J). By contrast, lymph node metastasis (P=0.274), administration of neoadjuvant chemotherapy (P=0.059), completeness of debulking (P=0.845) and postoperative chemotherapy (P=0.118) were not significantly associated with OS (Fig. 2B, F, G and I), although a trend toward worse survival was observed in patients receiving neoadjuvant chemotherapy. Across the majority of subgroups, median OS was not reached, except in patients with peritoneal carcinomatosis and recurrence, where the median survival was 48.0 months. Follow-up duration was broadly comparable between groups.

Univariate and multivariate Cox regression analyses of overall survival. According to univariate Cox regression analysis, advanced FIGO stage, omental metastasis, peritoneal carcinomatosis, ascites, residual disease and recurrence were significantly associated with worse OS. Residual disease (HR, 7.93; 95% CI, 2.51-25.02; P<0.001) and recurrence (HR, 10.06; 95% CI, 3.17-31.92; P<0.001) demonstrated the strongest associations with mortality (Table IV). In multivariate analysis, only residual disease remained an independent predictor of OS (adjusted HR, 5.59; 95% CI 1.44-21.66; P=0.013), while FIGO stage was no longer statistically significant (Table V).

Discussion

The present multicenter study reports, to the best of our knowledge, the first comprehensive overview of LGSOC in Indonesia including one of the largest cohorts reported from an LMIC. The findings confirm several established characteristics of LGSOC, including its occurrence in a relatively younger population in this setting and the substantial proportion of advanced-stage presentation. In this cohort, residual disease after surgery and advanced FIGO stage demonstrated the strongest unadjusted associations with recurrence and survival outcomes.

Compared with international cohorts, the studied Indonesian population demonstrated several distinct characteristics. The median age at diagnosis (45.5 years) was approximately a decade younger than the median of 54-56 years reported in Western and East Asian studies (3-6), suggesting potential demographic or referral differences within Indonesia, such as earlier onset or differences in health-seeking behavior. Despite the younger age, the proportion of patients diagnosed at advanced stages (III-IV; 50%) was comparable to global data, indicating that delays in presentation and diagnosis remain a universal challenge (10,11). Obesity and elevated CA-125 levels were common findings that paralleled those of other recent cohorts, highlighting their relevance as risk and prognostic factors (10,12). The overall rate of optimal cytoreduction (72.5%) was slightly higher when compared with several large single-center series (40-50%) (1,13), which may reflect differences in stage composition and the surgical focus of tertiary referral hospitals participating in the present study. Collectively, these observations illustrate how patient demographics, health-system factors and surgical centralization shape outcomes in an LMIC context. This younger median age may reflect Indonesia's population structure, which is demographically younger than the populations of several

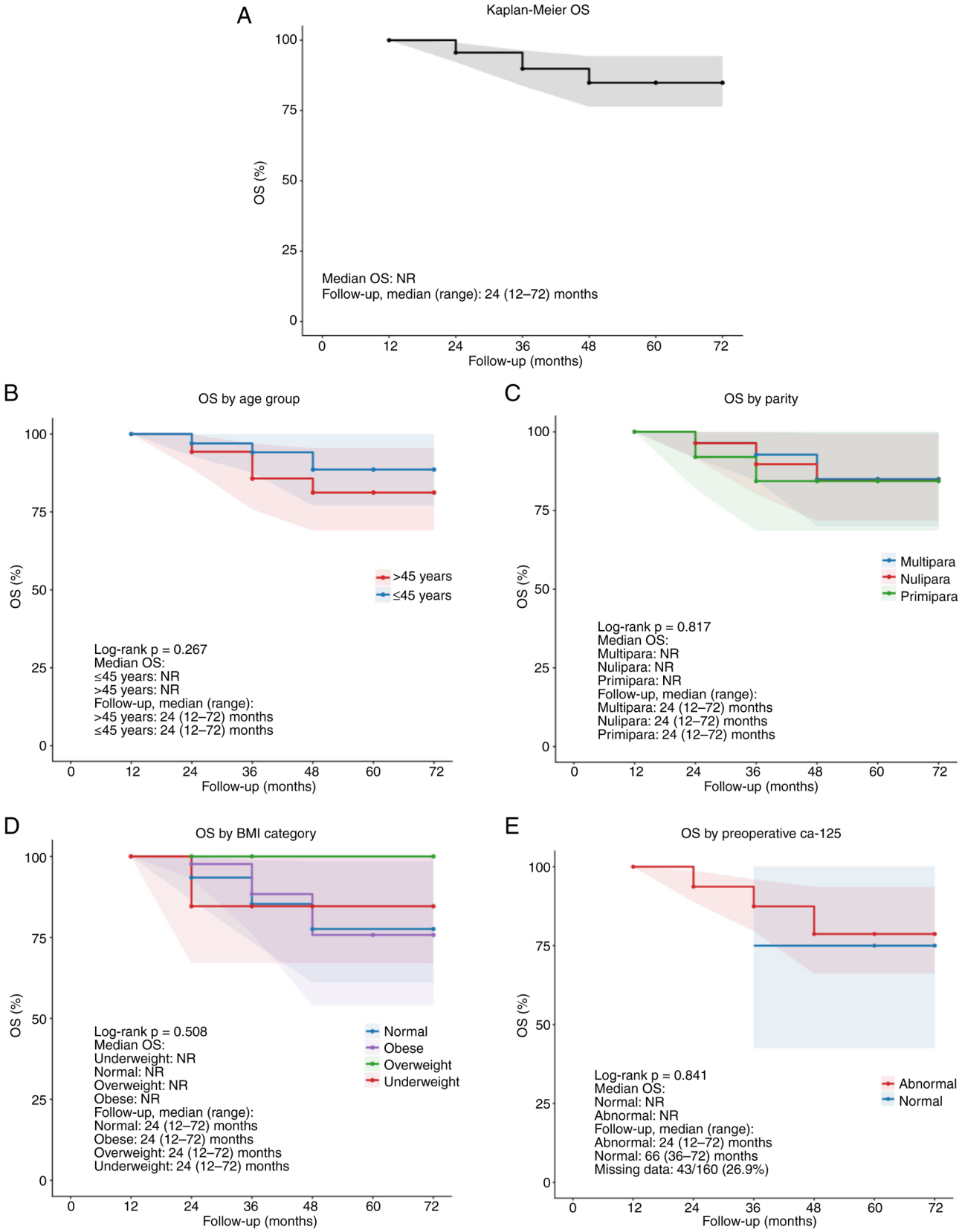

Figure 1. Kaplan-Meier curves for OS according to baseline clinical and demographic characteristics. (A) OS of the entire cohort. (B) Overall survival stratified by age group (≤45 vs. >45 years). (C) OS according to parity status. (D) OS across BMI categories. (E) OS stratified by preoperative CA-125 levels. No statistically significant differences in survival were observed across the evaluated subgroups (log-rank test). CA-125, cancer antigen-125; OS, overall survival; NR, not reached.

Western countries, as well as referral dynamics in which symptomatic younger patients are more likely to reach tertiary centers. Biological variation cannot be excluded; however, health-system factors likely have a substantial

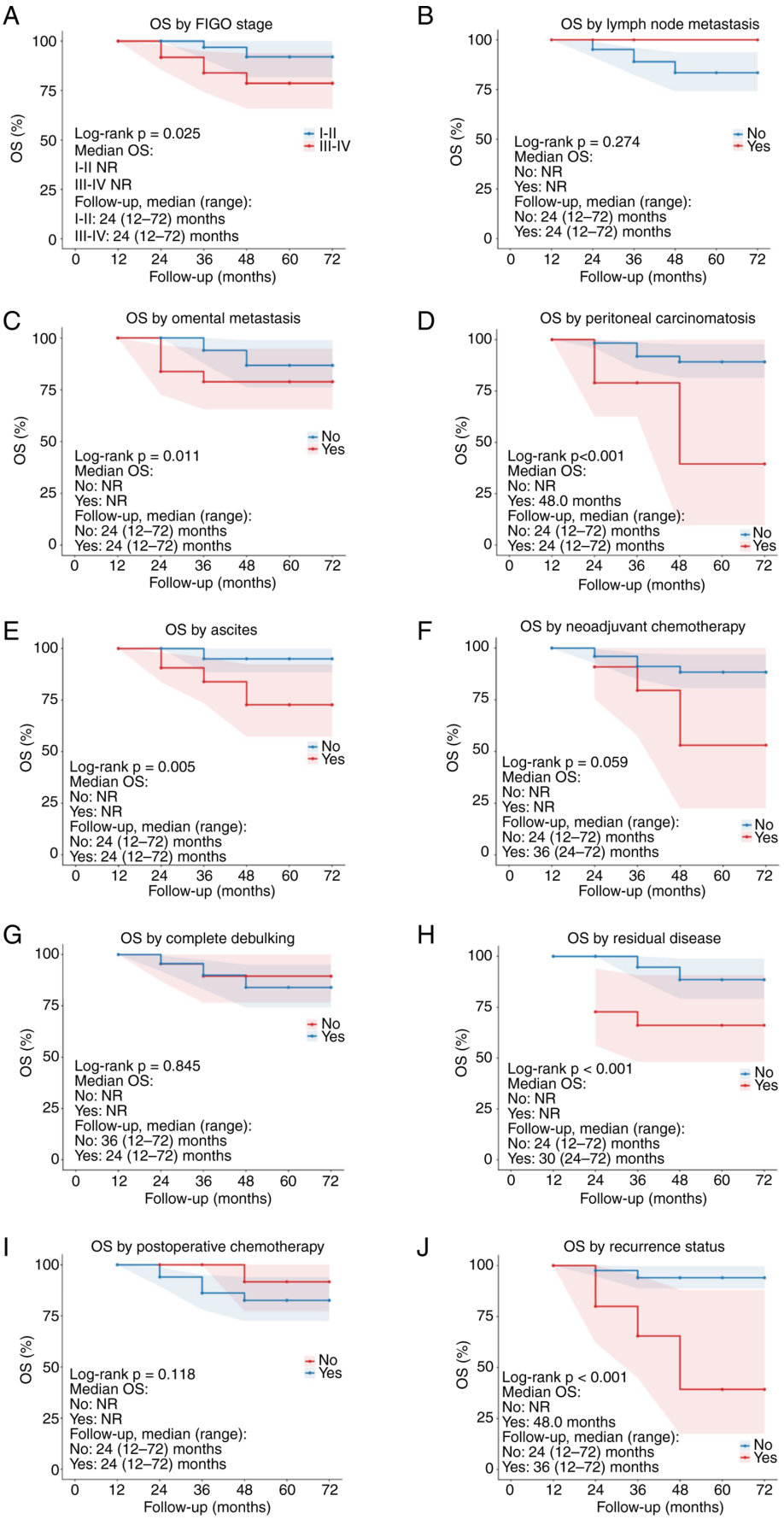

Figure 2. Kaplan-Meier OS analyses according to clinicopathological and treatment-related factors. (A) FIGO stage (I-II vs. III-IV). (B) Lymph node metastasis. (C) Omental metastasis. (D) Peritoneal carcinomatosis. (E) Ascites. (F) Neoadjuvant chemotherapy. (G) Completeness of debulking. (H) Residual disease. (I) Postoperative chemotherapy. (J) Recurrence status. Survival differences were assessed using the log-rank test. Significant differences in OS were observed for FIGO stage, omental metastasis, peritoneal carcinomatosis, ascites, residual disease and recurrence status. FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; NR, not reached.

Table IV. Univariate Cox regression analysis.

Variable	HR	95% CI	P-value
FIGO stage III-IV	4.82	1.05-22.05	0.042
Lymph node metastasis	-	-	0.998
Omental metastasis	3.97	1.26-12.53	0.018
Peritoneal carcinomatosis	6.42	2.00-20.59	0.002
Ascites	6.61	1.45-30.23	0.015
Neoadjuvant chemotherapy	3.34	0.90-12.41	0.072
Complete debulking	0.86	0.19-3.95	0.846
Residual disease	7.93	2.51-25.02	<0.001
Postoperative chemotherapy	0.23	0.03-1.75	0.154
Recurrence	10.06	3.17-31.92	<0.001

FIGO, International Federation of Gynecology and Obstetrics.

Table V. Multivariate Cox regression analysis.

Variable	Adjusted HR	95% CI	P-value
FIGO stages III-IV	2.05	0.34-12.27	0.433
Residual disease	5.59	1.44-21.66	0.013

FIGO, International Federation of Gynecology and Obstetrics.

effect on the observed differences between the findings of the present study and those of previous reports.

Notably, optimal cytoreductive surgery was achieved in 72.5% of cases, which is higher when compared with the rates reported in several single-center series (40-50%) (1). Although the definition of optimal cytoreduction required complete macroscopic clearance (no visible residual disease), the relatively high R0 rate is most plausibly explained by the inclusion of a substantial proportion of early-stage cases (50%) rather than superior surgical aggressiveness alone. Therefore, comparisons with cohorts composed predominantly of advanced-stage disease should be interpreted cautiously. Moreover, a direct comparison should consider differences in patient composition; 50% of the present cohort consisted of early-stage (I-II) disease, whereas several prior studies included predominantly advanced-stage cases (III-IV) (14,15). In addition, the definition of optimal cytoreduction required complete macroscopic clearance (no visible residual disease), compared with the <1 cm residual threshold used in several international reports (16,17). Although the present study adopted a stricter definition of optimal cytoreduction, the relatively high rate of optimal surgery (72.5%) is more plausibly explained by the inclusion of a large proportion of early-stage cases (50%) rather than by the definitional criterion itself. This emphasizes the importance of considering stage distribution when comparing surgical outcomes across studies. Schmeler and Gershenson (18) reported optimal cytoreduction in 40-50% of LGSOC cases using the <1 cm residual threshold, highlighting the uniqueness of the present findings under a strict definition. This is important because numerous studies have confirmed surgical completeness as the principal prognostic factor for LGSOC, overshadowing the modest impact of adjuvant chemotherapy owing to inherent chemoresistance in the tumor (11,13). The observed adoption of adjuvant chemotherapy (74.4%) fits with still-evolving standards; however, recent meta-analyses suggest that chemotherapy has limited benefits in LGSOC, with hormonal or targeted therapies emerging as promising alternatives (8,13). The acceptance and utilization of hormone maintenance therapy remained limited in the present cohort, suggesting an area for improvement in clinical practice according to updated global guidelines (1,13).

The most statistically significant predictors of recurrence and survival in the present cohort were residual disease after surgery and the FIGO stage at diagnosis, which mirrors the conclusions of recent global and multicenter studies (1,11,13). The present data showed that patients with advanced-stage disease were more likely to exhibit suboptimal debulking and worse survival than patients with early-stage disease, a relationship confirmed in major registries and surveillance, epidemiology and end results studies (11). These findings reinforce the interpretation that, unlike high-grade serous ovarian cancer, survival in LGSOC is more sensitive to the initial quality of surgical cytoreduction than to systemic therapy (1,13).

These findings were further supported by time-to-event analyses. KM curves demonstrated significantly worse OS among patients with advanced FIGO stage, omental metastasis, peritoneal carcinomatosis, ascites, residual disease and recurrence. In univariate Cox regression, these variables were significantly associated with an increased risk of mortality, with residual disease (HR, 7.93) and recurrence (HR, 10.06) demonstrating the strongest effects. In multivariate analysis, only residual disease remained an independent predictor of OS (adjusted HR, 5.59; 95% CI, 1.44-21.66; P=0.013), whereas FIGO stage lost statistical significance after adjustment. This finding suggests that the prognostic impact of disease stage may be partially mediated through surgical outcomes, reinforcing the key importance of complete cytoreduction in LGSOC (19).

A high CA-125 level at diagnosis, which was present in 70.6% of cases, is also a recognized independent prognostic factor of tumor burden and aggressiveness. However, its specific impact on OS may be less than that of stage or surgical success (11). Tumor size was not significantly associated with tumor stage or outcome in the present cohort, which agrees with recent reports highlighting the prognostic importance of residual mass and disease stage (1,11). Unlike some international studies that classify residual disease according to size (<1 cm vs. ≥1 cm), the present dataset only distinguished between 'no visible disease' and 'any visible residual disease'. This may partially explain the high rates of optimal cytoreduction. Nevertheless, interpretation of CA-125 findings should be cautious owing to the incomplete documentation in a subset of patients, which may introduce residual selection bias.

Emerging literature from the past 5 years also highlights the relevance of molecular targeted therapies, particularly the use of MEK inhibitors for MAPK pathway mutations, as superior or adjunctive options to chemotherapy in recurrent or refractory settings (1,8,13). The incorporation of

precision medicine remains rare in LMIC, including the present population, but warrants advocacy in tumor board decision making.

In the present cohort, the recurrence rate was 10, and 92.5% of patients were alive at the final follow-up point. However, the median follow-up duration of 24 months is relatively short for an indolent malignancy such as LGSOC, for which late recurrences are well documented. Consequently, the reported recurrence rate likely underestimates the true long-term recurrence burden in this population, and extended follow-up is necessary for more definitive survival assessment. Published international data have reported 5-year OS rates of 59-89%, depending on the stage and extent of cytoreduction (10,11,13). These findings collectively confirm that long-term outcomes in LGSOC are primarily driven by disease stage and surgical completeness. Patients with early-stage disease universally show good outcomes, highlighting the key importance of prompt diagnosis and aggressive surgery.

The present findings concur with the latest global evidence that achieving optimal cytoreductive surgery at the earliest stage is paramount for favorable outcomes in patients with LGSOC (20). Adjuvant chemotherapy, although common, provides limited benefits; thus, greater emphasis should be placed on potential hormone-based and targeted regimens, as supported by emerging evidence. Continued research, increased access to molecular diagnostics and adherence to consensus guidelines are required to improve the prognosis of patients with LGSOC, particularly in LMICs. Because follow-up durations varied across centers, long-term survival analysis was not feasible; nonetheless, the observed survival rate at the last follow-up supports the generally favorable prognosis of LGSOC.

Beyond reflecting global patterns, the present findings also highlight several features unique to the Indonesian population. Patients in this cohort were diagnosed nearly a decade earlier than international averages, and the study encompassed nine tertiary hospitals across seven provinces, representing a multiethnic population and variable access to oncology services. Such diversity reflects the real-world complexity of cancer care in Indonesia, an archipelagic nation where geographic distance and unequal referral systems can influence the stage at diagnosis and surgical outcomes.

Structural limitations within the healthcare system likely contribute to these disparities. The distribution of obstetricians and gynecologists remains uneven, with workforce shortages and a tendency to concentrate in densely populated regions, leaving a proportion of hospitals without adequate specialist coverage (21). Moreover, the presence of specialists alone does not ensure access to high-quality oncological care, as resource constraints, limited availability of advanced therapies and gaps in training may hinder optimal management (22). These challenges are further compounded by the scarcity and geographic concentration of gynecological oncologists, with only 139 specialists nationwide and the majority located in Java, resulting in substantial barriers to timely diagnosis and treatment, particularly in remote regions (23).

Within the national health insurance system of Indonesia, the tiered referral pathway may also contribute to delays in diagnosis and treatment, creating a cascade of care that disproportionately affects rare malignancies such as LGSOC, which may remain underdiagnosed and present at more advanced stages. Collectively, these findings underscore the importance of strengthening specialist distribution, referral systems and oncology infrastructure to improve equitable cancer care delivery in LMIC settings.

The present study has several limitations. Ethnicity and geographic distance to referral centers were not captured in this dataset; however, given the multiethnic composition and wide geographic distribution of Indonesia, these factors are expected to contribute to variations in the stage at diagnosis and treatment access. Formal analyses of OS and disease-free survival could not be performed because of variability and incompleteness in follow-up documentation across centers, a common limitation in multicenter retrospective studies. First, as a retrospective analysis relying on heterogeneous electronic medical records across multiple centers in Indonesia, certain variables such as BMI, CA-125 levels and tumor size were incompletely documented. In addition, the limited number of recurrence (n=16) and mortality events (n=12) constrained the statistical power of survival analyses and restricted the complexity of multivariate modeling.

Despite these limitations, KM survival analysis with log-rank testing and Cox proportional hazards regression were performed to explore survival patterns and estimate effect sizes. Given the small number of events, the multivariate model was intentionally restricted to a limited number of clinically relevant covariates to reduce the risk of overfitting; therefore, the findings should be interpreted as exploratory rather than definitive independent predictors.

Molecular profiling data, including KRAS, BRAF and NRAS mutation status as well as hormone receptor expression, were unavailable in this retrospective cohort. Given that 40-50% of LGSOC tumors harbor MAPK pathway alterations, the absence of molecular characterization limited the assessment of eligibility for targeted therapies such as MEK inhibitors. Future prospective registries incorporating molecular data will be essential to align national management strategies with contemporary precision oncology approaches.

Future research should prioritize improving the quality and completeness of clinical documentation and establishing a national ovarian cancer registry in Indonesia. These efforts would enable robust survival analyses, support evaluation of treatment patterns and facilitate the integration of molecular and genomic data. In addition, such infrastructure would allow meaningful collaboration with international datasets, enabling comparative analyses of surgical outcomes, referral patterns and treatment effectiveness across different healthcare settings.

From a clinical perspective, strengthening the centralization of cytoreductive surgery in high-volume gynecological oncology centers is essential to improve surgical outcomes. The development of structured referral pathways from secondary and district hospitals may reduce delays in treatment and increase the likelihood of optimal cytoreduction. Expanding access to hormonal and targeted therapies, including MEK inhibitors, should also be prioritized to improve outcomes in patients with LGSOC.

From a policy standpoint, these findings support national strategies aimed at improving early detection and timely

referral. Public awareness initiatives targeting persistent abdominal symptoms may contribute to earlier diagnosis and reduce the proportion of patients presenting with advanced-stage disease. Collectively, these efforts highlight the importance of coordinated clinical, research and policy approaches to improve outcomes for patients with LGSOC in resource-limited settings.

In conclusion, the present large multicenter Indonesian cohort study revealed that the ability to achieve complete surgical cytoreduction without residual disease was the most potent predictor of favorable outcomes. The present findings advocate for national health strategies focused on improving early detection and ensuring that patients with LGSOC are managed in specialized centers with the surgical expertise required to maximize their chances of optimal surgical outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BAT, KN, RAU, SR, FE, KYS, TMI, TWU, STW, HMARP and ER contributed to conceptualization. KN, RAU and HAS confirm the authenticity of all the raw data; BAT, KN and RAU contributed to formal analysis; BAT, KN and RAU contributed to investigation. BAT, KN, RAU and HAS contributed to methodology design. RAU contributed to project administration. WS, SR, FE, KYS, TMI, VGEP, TWU, TDA, STW, HMARP and ER contributed to data collection at each central hospital. BAT and WS supervised the study. BAT and KN contributed to validation. BAT, KN, RAU and HAS wrote the original draft. All authors reviewed and edited the manuscript, and read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Dr. Soetomo General Academic Hospital (approval no. 1095/KEPK/IX/2024; Surabaya, Indonesia). All data used in the present study are available for independent analysis for the purposes of additional data analysis or to ensure reproducibility of the present study in other centers. Informed consent for participation was waived in accordance with the approval granted by the institutional ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript and to enhance the literature search, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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