Prognostic Impact of Baseline Serum Creatinine in Patients with Advanced High-Grade Serous Ovarian Carcinoma Undergoing Neoadjuvant Chemotherapy

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ABSTRACT

Objective: To evaluate whether baseline serum creatinine is associated with survival outcomes in patients with advanced high-grade serous ovarian carcinoma undergoing neoadjuvant chemotherapy.
Methods: We retrospectively analyzed 77 patients treated between 2009 and 2018. Patients were stratified by baseline serum creatinine levels (<84 vs. ≥84 µmol/L), and survival outcomes were assessed using Kaplan-Meier analysis.
Results: No statistically significant differences in progression-free or overall survival were observed between groups. A trend toward shorter OS in the elevated creatinine group did not reach significance.
Conclusion: Baseline serum creatinine was not found to be a statistically significant prognostic marker in this cohort. These results highlight the need for adjusted analyses incorporating established prognostic factors in future research.

KEYWORDS

ovarian cancer; neoadjuvant chemotherapy; serum creatinine; prognosis

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INTRODUCTION

In patients newly diagnosed with advanced high-grade serous ovarian, tubal, or peritoneal carcinoma deemed primarily inoperable, neoadjuvant chemotherapy is the standard treatment approach. Typically, 3–4 cycles of combination chemotherapy with paclitaxel and carboplatin are administered, with the exact number depending on tumor response and assessment of operability prior to planned interval debulking surgery. For patients with poorer performance status and significant comorbidities, carboplatin monotherapy may be considered, with priority given to maintaining dose intensity, such as through weekly regimens. Prior to each chemotherapy cycle, standard laboratory assessments include complete blood count, electrolytes (sodium, potassium, chloride), urea, creatinine, uric acid, bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). These parameters are crucial not only for determining the appropriate dose of carboplatin but also for monitoring potential adverse effects of systemic treatment, such as anemia, nausea, vomiting, or deterioration of renal function.

Previous studies have demonstrated that overall health status and performance status (PS) significantly influence both progression-free survival (PFS) and overall survival (OS) (1). At some institutions, the KELIM score is currently employed as a predictor of resistance to platinum-based therapies, significantly influencing PFS and OS. This score is also important for planning subsequent treatments, such as maintenance therapy with PARP inhibitors (2). Several prior studies have evaluated the prognostic significance of serum creatinine levels across various malignancies, including colorectal cancer, prostate cancer, and urothelial carcinoma (3–5).

It is therefore hypothesized that elevated serum creatinine, indicative of impaired renal function, might adversely affect the prognosis of patients with advanced high-grade serous ovarian carcinoma by necessitating dose reductions or premature discontinuation of chemotherapy. This retrospective cohort study aimed to investigate whether baseline serum creatinine levels serve as an additional prognostic parameter affecting PFS and OS in stage III and IV patients undergoing neoadjuvant chemotherapy.

METHODS

STUDY POPULATION AND DATA COLLECTION

This retrospective, single-center cohort study included 77 patients with histologically confirmed advanced high-grade serous ovarian, tubal, or peritoneal carcinoma treated between 2009 and 2018. Inclusion criteria were: completion of four cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel, interval debulking surgery, and at least four cycles of postoperative chemotherapy. Patients who discontinued treatment prematurely due to disease progression, toxicity, surgery ineligibility, or incomplete data were excluded. This selection was made to ensure a homogeneous cohort with consistent treatment exposure, reducing potential confounding factors and increasing the validity of comparisons.

The primary aim was to evaluate whether baseline serum creatinine levels predict oncologic outcomes. Patients were stratified into two groups according to their baseline serum creatinine: those with levels below 84 μmol/L and those with levels equal to or above 84 μmol/L, in accordance with the local reference range. The primary endpoints were progression-free survival (PFS) and overall survival (OS), measured from the date of diagnosis to the date of radiologically confirmed progression or death, respectively.

Baseline serum creatinine levels were obtained from hospital electronic medical records (NIS, Medicalc) at the time of the first neoadjuvant chemotherapy cycle. Diagnosis date, date of disease progression (based on CT imaging), and date of death were retrieved to assess PFS and OS.

Patient characteristics such as age, menopausal status, hormone replacement therapy (HRT) use, parity, CA-125 level, BMI, FIGO stage (III vs. IV), and postoperative surgical residuum were also collected. FIGO staging and residual tumor status were confirmed from surgical and pathological reports. Optimal cytoreduction was defined as R0 (no macroscopic residual tumor) or R1 (macroscopic residual tumor <1 cm); suboptimal cytoreduction was defined as R2 (macroscopic residual tumor ≥1 cm).

Statistical analyses were performed using NCSS 2023 software (NCSS, LLC., Kaysville, Utah, USA). Descriptive statistics were presented as absolute and relative frequencies for categorical variables, and means or medians with range for continuous variables. Kaplan-Meier survival analysis and log-rank tests were used to evaluate PFS and OS. Differences in categorical variables (FIGO stage, surgical residuum) between creatinine groups were evaluated using Fisher's exact test. Significance was set at $\alpha = 0.05$. A post hoc power analysis was conducted using a two-sided comparison of means based on the observed 6-month difference in overall survival between groups. The standard deviation (SD = 4.7 months) was calculated directly from the distribution of overall survival in the study cohort.

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital Hradec Králové. The requirement for individual informed consent was waived due to the retrospective design and anonymized data handling.

SERUM CREATININE ASSESSMENT

Measurement of serum creatinine (S-crea) is part of routine daily clinical practice. It is a cost-effective and commonly used method, although its interpretation can be challenging. Clinicians recognize that serum creatinine levels are influenced by muscle catabolism and can thus be either decreased or increased under various conditions such as anorexia, obesity, or after physical exertion. Identical serum creatinine values can correspond differently to glomerular filtration rate (GFR), which depends on gender, age, height, weight, and ethnicity (6). Physiologically

and pathophysiologically, creatinine secretion occurs in the renal tubules, explaining why creatinine clearance often overestimates the actual GFR. This overestimation can be unpredictable and may fluctuate over time in individual patients (7). Serum creatinine levels are also affected by patient nutrition, particularly a protein-rich diet. Nutritional enteral support with high protein content, which many patients receive, should also be considered (8). Additionally, literature describes extrarenal creatinine clearance by intestinal bacteria, contributing to reduced excretion, especially in patients with chronic kidney disease (9). Establishing correct reference intervals is difficult due to variations influenced by age, gender, and ethnicity. These variations were addressed by Pottel et al., who established age – and gender-specific intervals, mainly for the Caucasian population. Serum creatinine physiologically declines after birth, subsequently increases linearly with age, and remains relatively constant between 20–70 years of age in healthy individuals. In women over 70 years, serum creatinine levels physiologically increase (10). Tracking serum creatinine trends over time in individuals, particularly older adults, is more advantageous than relying solely on a single measurement, although even one measurement can indicate potential renal dysfunction (11).

Serum creatinine was measured using a COBAS 8000 analyzer (Roche, Mannheim, Germany) in the certified laboratory at University Hospital Hradec Králové. The enzymatic method employed involves converting creatinine to glycine, formaldehyde, and hydrogen peroxide through enzymes creatininase, creatinase, and sarcosine oxidase. Released hydrogen peroxide reacts catalytically with peroxidase, 4-aminophenazone, and HTIB to form a quinoneimine chromogen. The color intensity of this chromogen is directly proportional to the creatinine concentration in the reaction mixture. The local laboratory reference range for women is 45–84 µmol/L.

RESULTS

DESCRIPTIVE STATISTICS

Baseline characteristics stratified by serum creatinine are presented in Table 1. The median age was 64 years (range 31–87) in the normal creatinine group and 66 years (range 40–85) in the elevated group, with mean ages of 63.8 (SD 9.2) and 65.0 (SD 8.8), respectively. Postmenopausal status predominated in both groups (95% vs. 94%). Hormone replacement therapy use was reported in 7% of the normal group and 6% of the elevated group.

The median baseline CA-125 level was 1043 kU/L in the normal creatinine group and 1132 kU/L in the elevated group. Median BMI was comparable (25.6 vs. 26.0 kg/m²). Suboptimal cytoreduction (R2) occurred in 31% of patients with normal creatinine versus 78% in the elevated group. R0 resection was achieved in 49% and 22%, respectively, while no R1 resections occurred in the elevated creatinine group.

FIGO stage III disease was present in 80% of the normal creatinine group and 83% of the elevated group. Stage IV was found in 20% and 17%, respectively. Smoking prevalence was 7% versus 11%, arterial hypertension was noted in 22% versus 28%, and diabetes mellitus in 14% versus 22%, for the normal and elevated creatinine groups, respectively.

GROUP STRATIFICATION AND OUTCOMES

Patients were divided into two groups based on baseline serum creatinine (S-crea): those with levels <84 µmol/L (normal range) and those with levels ≥84 µmol/L. There were 59 patients (76.62%) in the normal S-crea group and 18 patients (23.38%) in the elevated S-crea group. Among the patients with normal S-crea, 80% had stage III and 20% had stage IV; among those with elevated S-crea, 83% had stage III and 17% had stage IV. There was no significant

Tab. 1 Descriptive parameters and their frequencies in the study cohort.

Parameter	Normal S-crea <84 µmol/L (n=59)	Elevated S-crea ≥84 µmol/L (n=18)
Age in years	Median 64 (range 31–87) Mean 63.8 (SD 9.2)	Median 66 (range 40–85) 65 (SD 8.8)
Menopausal status	Premenopausal: 3 (5%) Postmenopausal: 56 (95%)	Premenopausal: 1 (6%) Postmenopausal: 17 (94%)
HRT use	4 (7%)	1 (6%)
CA-125 (kU/L)	Median 1043	Median 1132
BMI (kg/m²)	Median 25.6	Median 26.0
Postoperative residuum	R0: 29 (49%), R1: 12 (20%), R2: 18 (31%)	R0: 4 (22%), R1: 0 (0%), R2: 14 (78%)
FIGO stage	III: 47 (80%), IV: 12 (20%)	III: 15 (83%), IV: 3 (17%)
Smoking	4 (7%)	2 (11%)
Arterial Hypertension	13 (22%)	5 (28%)
Diabetes mellitus	8 (14%)	4 (22%)

difference in FIGO stage distribution between the two creatinine groups (p = 0.462).

In terms of surgical outcomes, 69.5% of patients in the normal S-crea group had R0/R1 resection compared to 44.4% in the elevated S-crea group. Conversely, 30.5% of the normal S-crea group and 55.6% of the elevated group had R2 resection. This difference was not statistically significant (p = 0.120), although a trend toward worse surgical outcome in the elevated creatinine group was noted.

Regarding survival outcomes, there was no statistically significant difference in PFS between the two groups. The median PFS was 14 months (95% CI: 13–17) in the normal creatinine group compared to 12 months (95% CI: 9–15) in the elevated creatinine group (p = 0.951). Similarly, OS was not significantly different, although numerically shorter in the elevated creatinine group. The median OS was 31 months (95% CI: 22–41) in the normal group compared to 25 months (95% CI: 14–32) in the elevated group (p = 0.316). Figure 1 and Figure 2 presents the PFS and OS, respectively. A post hoc power analysis based on the observed OS difference (31 vs. 25 months) and the calculated SD of 4.7 months indicated a statistical power of 99.7%, suggesting a very low probability of Type II error.

DISCUSSION

This retrospective single-center study investigated whether baseline serum creatinine levels have prognostic value in patients with advanced high-grade serous ovarian carcinoma undergoing neoadjuvant chemotherapy. Although the differences did not reach statistical significance, patients with elevated creatinine levels had numerically shorter progression-free and overall survival, as well as a higher rate of suboptimal cytoreduction (R2). These findings suggest that serum creatinine may reflect underlying physiological vulnerability or treatment tolerance, and therefore may hold potential as a supportive prognostic marker.

Our data showed that patients with elevated serum creatinine were less likely to achieve optimal cytoreduction. While 69.5 percent of patients with normal creatinine levels underwent R0 or R1 resection, only 44.4 percent in the elevated creatinine group did so. Conversely, the rate of suboptimal cytoreduction (R2) was higher in the elevated creatinine group. Although the difference was not statistically significant, this trend may indicate impaired surgical outcomes in patients with compromised baseline renal function. A similar trend was observed in overall survival, where patients with elevated creatinine had a median OS of 25 months compared to 31 months in the normal group. These associations, while not conclusive, are clinically relevant and warrant further investigation.

In recent years, interest has grown in identifying pre-treatment laboratory markers that reflect systemic inflammation, nutritional status, or comorbidity burden. Studies have shown that markers such as IL-37 and plasma fibrinogen may outperform traditional tumor markers like CA-125 in prognosticating advanced epithelial ovarian cancer (12, 13). These data support the notion that simple blood-based biomarkers can contribute to risk stratification. Nutritional status is also known to impact outcomes. Low albumin levels, for example, have been linked to delayed wound healing, which in turn may postpone adjuvant chemotherapy and negatively affect prognosis (14). Creatinine levels, although primarily associated with renal function, are also influenced by muscle mass and protein intake, both of which relate closely to nutritional status and frailty. Emerging evidence also points to the role of physical activity in improving cancer outcomes. Kanbay et al. demonstrated that exercise reduces inflammation and oxidative stress while enhancing cardiovascular function and immune competence, all of which are likely to contribute to improved tolerance of systemic treatment and potentially better survival (16).

This study has several limitations, primarily its retrospective design, which restricts control over confounding factors. BRCA mutation status was unavailable for most patients, as routine testing was only implemented later in the study period. Although the cohort size was modest, a post hoc power analysis based on patient-level survival data (α = 0.05, pooled SD = 4.7 months, n = 59 vs. 18) demonstrated approximately 99.7% power to detect the observed 6-month OS difference. This suggests that the lack of statistical significance is unlikely to be due to insufficient sample size. However, given the inherent limitations of retrospective analyses, these findings should be interpreted with caution and validated in prospective studies.

In light of our findings, serum creatinine may not serve as a standalone prognostic factor, but rather as a surrogate

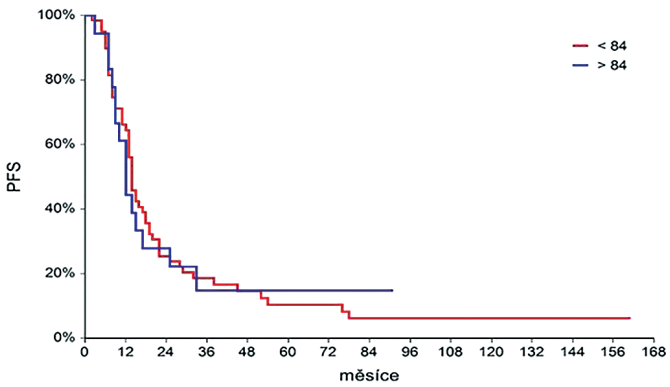

Fig. 1 Progression-free survival (PFS).

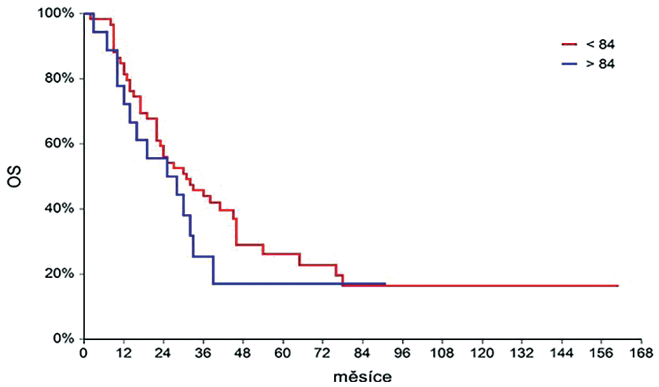

Fig. 2 Overall survival (OS).

for broader patient-related variables such as comorbidities, nutritional state, and functional reserve. The observed trends highlight the need for prospective studies to determine whether baseline creatinine, in combination with other biomarkers, could reliably support clinical decision-making in this population.

CONCLUSIONS

Our retrospective study found a non-significant trend toward shorter survival in patients with elevated baseline serum creatinine undergoing treatment for advanced ovarian cancer. While not sufficient to establish serum creatinine as an independent prognostic factor, these findings warrant further prospective evaluation of its potential role in combination with other clinical and biochemical markers.

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