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Review

Postoperative Admission in Critical Care Units Following Gynecologic Oncology Surgery: Outcomes Based on a Systematic Review and Authors' Recommendations

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Abstract. *Background/Aim: The present study aimed to evaluate the predictors of admission to the Critical Care Units (CCUs) and factors predisposing to prolonged stay in CCUs after gynecological oncology surgery. Patients and Methods: Studies which addressed cases of women who underwent surgery for gynecological malignancies and required postoperative CCU admission were included. Results: Seven studies with 3820 patients were included. Among them, 1680 required admission to CCU. Advanced age, higher Charlson Comorbidity Index (CCI) score, longer operative times, protracted blood loss and intestinal resection were associated with higher probability of CCU admission. Patients' age, operative times, blood loos and intestinal resection were significant predictors of prolonged stay to CCUs. Conclusion: Admission to CCU and length of stay following surgery for gynecologic malignancies is driven by specific patient characteristics as well as intraoperative values. Further studies are needed to validate high risk patients who will benefit from postoperative care to CCUs to ensure favorable postoperative outcomes and cost-effectiveness.*

Advances in surgical techniques, anesthetics and critical care management as well as the development of specialized centers for the management of gynecologic oncology patients, during the past decades, have resulted in improved outcomes following surgical procedures, which have been considered the gold standard for the management of a significant proportion of gynecological cancer patients at various stages. For patients with advanced stage tumors that are considered resectable, extensive cytoreductive procedures are required with the intention to achieve complete cytoreduction (1). Elevated rates of perioperative morbidity and mortality have been reported in these patients and have been mainly associated with either the patients' past medical history and performance status or the type of surgery and the underlying malignant disease or with a combination of those factors (2, 3). Therefore, critical care management is critical for surgically managed patients with the intent to establish a closer monitoring and to prevent or treat postoperative complications (4). Intensive monitoring of gynecologic oncology patients in the postoperative setting is implemented in various types of critical care units (CCUs) which include post anesthesia care units (PACU), high dependency units (HDU), surgical intensive care units (SICU) and intensive care units (ICU) (5).

Routine postoperative admission to the ICU has been used by several institutions especially in cases of debulking surgery for advanced ovarian cancer or radical exenteration procedures for cervical cancer which require prolonged and complex surgical procedures (2). A number of studies have focused on the cost-effectiveness of utilizing CCUs as a routine after major surgeries while simultaneously attempt to designate the selection criteria for patients who require admission to CCU and evaluate the pre-and perioperative factors that predispose to admission to CCUs (6, 7).

The objective of our study was to review and present the current knowledge on the predictors of admission to the CCUs and evaluate the factors that predispose to prolonged stay in CCUs after gynecological oncology surgery.

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Key Words: Critical care unit, intensive care unit, gynecologic oncology, cytoreduction, surgical intensive care unit.

Patients and Methods

Study design. The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines based on the authors' predetermined eligibility criteria (8). All appropriate prospective and retrospective clinical trials, which addressed cases of women who underwent surgery for the management of gynecological malignancies and required postoperative admission in any type of CCU were considered eligible for inclusion in the present systematic review. Inclusion criteria were as follows: publications with >20 patients, studies published up to 31/12/2019, studies published in any language, patients' age ≥18 years, patients with confirmed gynecologic malignancy, surgical procedures performed either through laparotomy or laparoscopy, outcomes for at least one perioperative predictor/indication of ICU admission. Reviews and animal studies were excluded from analysis and tabulation. Additional exclusion criteria were as follows: admission to CCU for any reason prior to surgery, admission to CCU for benign gynecological diseases, insufficient data, cases not managed by gynecologic oncologist and patients admitted to CCU but were managed for their disease with strategies other than surgery (*i.e.* chemotherapy). Three authors (AP, NT and DH) independently and meticulously searched the literature, excluded overlaps, and tabulated the selected indices in structured forms. All discrepancies during the data collection, synthesis, and analysis were resolved by the consensus of all authors.

Search strategy and data collection. We systematically searched the literature for articles published up to May 2020 using PubMed (1966-2020), Scopus (2004-2020), and Google Scholar (2004-2020) databases along with the references of the articles which were retrieved in full text. The following key words were used for the search: "gynecologic malignancy", "gynecologic cancer", "gynecologic surgery", "intensive care unit" "critical care unit", "high dependency unit". A minimum number of search keywords were utilized in an attempt to assess an eligible number that could be easily searched while simultaneously minimizing the potential loss of articles. The PRISMA flow diagram schematically presents the stages of article selection (Figure 1).

Data on patient characteristics included type of malignancy, indications of ICU admission, age, BMI, disease stage, Charlson Comorbidity Index (CCI) and neoadjuvant chemotherapy (NACT) administration. Concerning the main findings of the study, perioperative outcomes such as operative time, estimated blood loss (EBL), length of stay (LOS) to ICU, intestinal surgery, complications and readmissions were appraised. Moreover, survival outcomes if available were also evaluated.

Results

Included and excluded studies. A total of 7 studies which comprised 3820 patients who underwent surgery for the management of gynecological malignancies were included (9-15). Among them, 1680 required admission to ICU whereas the remaining 2140 were followed-up in gynecological departments.

Six studies were excluded from the present systematic review (16-21). Among them, three were excluded due to insufficient data concerning the evaluation of ICU-admission predictors (16, 17, 20), while another study was not included due to the fact that it included patients with malignant and benign diseases and no separate data for malignancies was available (19). The study by Kathiresan *et al*. was excluded due to lack of data concerning the specific number of patients included which was not identified even after our attempt to contact the authors (18). In the study by Abbas *et al*., analysis was restricted only to patients with ICU stay of more than three days and therefore it was excluded (21).

Indicators and predictors of ICU admission (ICU vs. no-ICU). A total of 4 studies evaluated perioperative outcomes of 2626 patients who underwent surgery for gynecologic malignancies and were compared on the basis of admission to the ICU or not (9, 10, 12, 14). Among them, 486 required postoperative ICU (ICU group) admission whereas the remaining 2140 received standard postoperative care in gynecologic clinic (non-ICU group). The main characteristics of the included studies and the enrolled patients are shown in Table I. The most common gynecologic malignancy was ovarian cancer which was the primary indication of surgery in 2497 of the included patients. Advanced stage ovarian disease (III-IV stage according to FIGO classification) was detected in 82.5% (895/1085) patients. The most prevalent indication for ICU admission was hemodynamic instability and fluid management (56%, n=109/194) followed by the need of respiratory status management (30%, n=58/194). Other less prevalent reported indications included the cardiac, infections, neurologic, renal and endocrine disorders or any other combination of the aforementioned factors (9, 10, 12).

Mean age of patients ranged from 64 to 66 years in the ICU group and from 57 to 63 in the non-ICU group. A significant older age of patients admitted to the ICU was reported by three of the included studies (9, 10, 14). Twenty two out of 151 patients (14.6%) in the ICU-group received neoadjuvant chemotherapy (NACT) compared to 333 out of 808 (41.2%) in the non-ICU group. Patients who received NACT were less likely to be admitted to the ICU compared to those who did not receive NACT as reported by Ross *et al*. and Pepin *et al*. (9, 10). The Charlson Comorbidity Index (CCI) score was available for 3 of the included studies (10, 12, 14). Among them, the CCI score was considered as a significant factor for ICU admission either in uni-or in multivariate analysis in two studies (12, 14) while the other study did not found a difference (10). Patients in the ICU group had significantly prolonged operative times compared to the non-ICU group; the mean operative times ranged from 150 min to 283 min in the ICU group and from 127.5min to 211min in the non ICU group (9, 12). The same was observed in the case of estimated blood loss which was considered a significant predictive

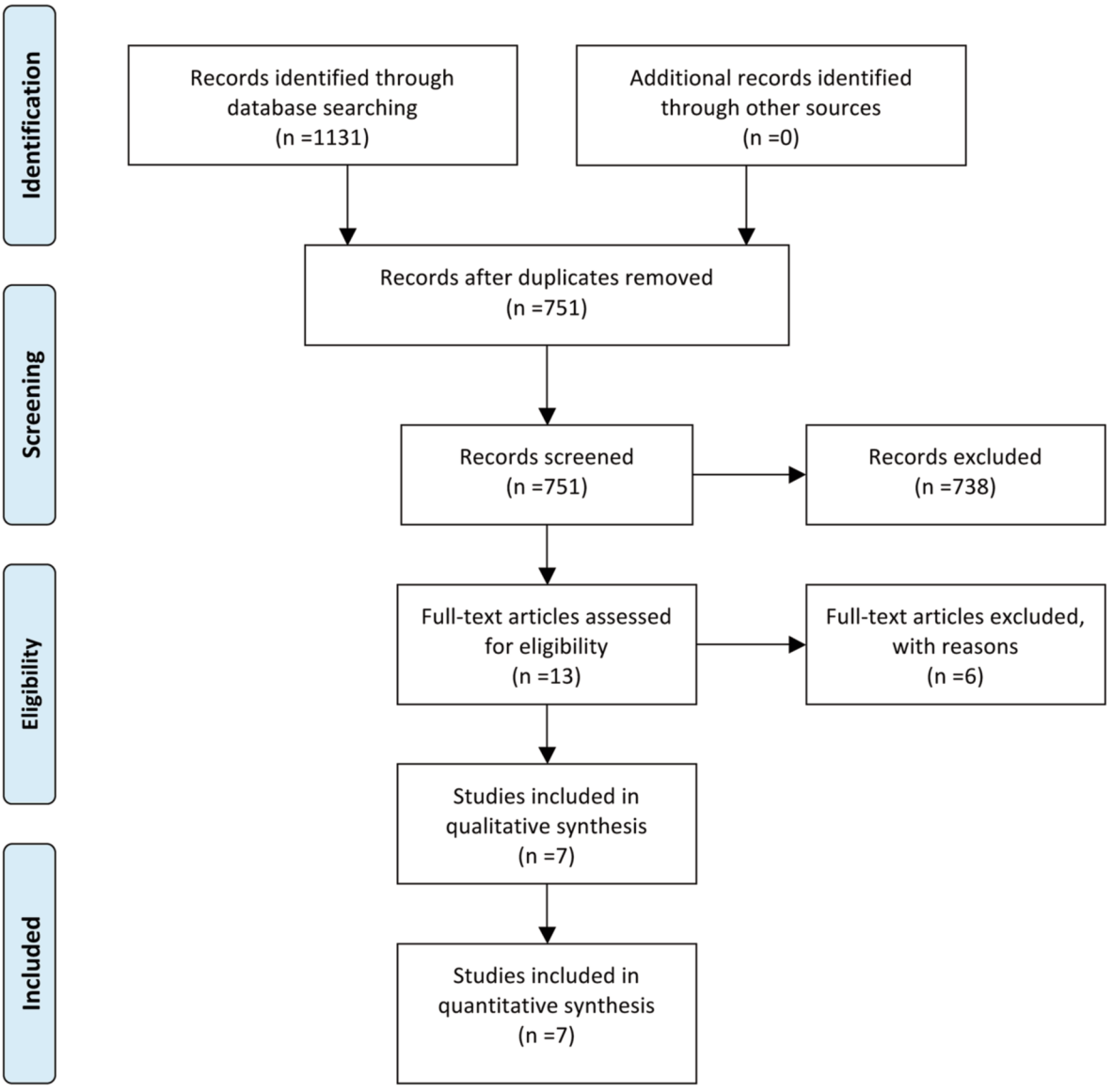

Figure 1. *Search flow diagram*.

factor of admission to the ICU, as reported by two of the included studies (9, 10).

A prolonged length of stay (LOS) was also observed by Ross *et al*. and Pepin *et al*. (9, 10) whereas Brooks *et al*. noted a significant difference in mean LOS among patients who finally died of the disease and were admitted to the ICU and those not admitted to the ICU (mean LOS 19 *vs*. 8 days) (14). Additionally, concurrent intestinal resection was considered a significant predictor for ICU admission; The proportion of patients who underwent any kind of intestinal operation in the ICU group was 44.7% (n=217/486) compared to 21.3% (n=455/2140) in the non-ICU group. Pepin *et al*. and Ross *et al*. have reported significantly elevated rates of hospital re-admission in the ICU-group ($p<0.01$ and $p=0.048$, respectively) (9, 10). Accordingly, multivariate analysis by Pepin *et al*. revealed that ICU admitted patients were more likely to be readmitted to hospital and presented postoperative complications ($p=0.041$ and $p<0.001$, respectively) (10). Despite the fact that Ross *et al*. have reported no difference in progression-free survival (PFS) among the two groups, overall survival (OS) in the ICU group was significantly shorter compared to the non-ICU group ($p<0.001$, HR=2.16, 95%CI=1.53-3.05) (9). The same was noted by Ruskin *et al*. who found a significant difference in disease-specific survival in ICU admitted compared to non-ICU patients (median 34 *vs*. 48 months, $p=0.007$) (12).

Table I. *Study and patient characteristics (ICU vs. non-ICU).*

Year; Author	2018; Ross	2017; Pepin	2011; Ruskin	2002; Brooks
Type of study	RS Matched 2:1	RS	RS	RS
Inclusion criteria	PDS; no preoperative ICU admission; procedure performed by gynaecologist oncologist; no preoperative plan of ICU admission	Surgical cytoreduction; advanced stage tumors; no germ cell and borderline tumors; no exclusive chemotherapy	Laparotomy for staging or debulking; no conversion form laparoscopy to laparotomy	Oophorectomy for OC
Type of malignancy	OC; fallopian carcinoma; primary peritoneal cancer	Stage III-IV epithelial OC; fallopian tube and primary peritoneal cancer	OC 126/255(49.4%); advanced stage disease OC; endometrial cancer (32.9%); peritoneal sarcoma (45)	OC
Indication for ICU admission	Hemodynamic instability: 54 (50%); respiratory failure: 38 (35.2%); Cardiac 18 (16.7%); Multiple admissions: 14 (13%) Infectious: 10 (9.3%); Abdominal process: 8 (7.4%); Other: 12 (11.1%)	Hemodynamic monitoring/ pharmacologic blood pressure support 36/43 (84.1%), respiratory failure/inability to extubate 10/43 (22.7%), bacteremia/sepsis (18.2%), anastomotic leak (9.1%), cardiac indication (4.6%), neurologic indication (4.5%) open abdomen (4.5%)	fluid management 19/43 (44.2%), respiratory status 10/43 (23.3%), cardiac complications (4.7%). multiple indications (25.6%)	N/A
Patient No	108 *vs.* 216	43 *vs.* 592	43 *vs.* 212	292 *vs.* 1120
Age (years)	66 (56.6-74)[c] *vs.* 61 (52.5-71)[c]	64 (39-79)[b] *vs.* 63 (26-93)[b]	64d *vs.* 59[d]	64±13.9[a] *vs.* 57±15.5[a]
NACT	10/108 *vs.* 39/216, $p<0.05$	12/43 *vs.* 294/592, $p<0.0001$	N/A	N/A
Charlson comorbidity index (CCI)	N/A	0: 62 *vs.* 26 1: 128 *vs.* 97 2: 166 *vs.* 158 <8: 26/43 *vs.* 356/592 3: 135 *vs.* 7 ≥4: 101 *vs.* 10 ≥8 17/43 *vs.* 236/59	<8: 20 *vs.* 45 ≥8 23 *vs.* 167	15±7.7[a] *vs.* 9±7.7[a]
Operative time (min)	150 (120-220)[c] *vs.* 127.5 (110-160)[c]	N/A	283[d] *vs.* 211[d]	N/A
Blood loss (ml)	700 (300-1025)[c] *vs.* 300 (200-500)[c]	1630 (1181-2147)[e] *vs.* 503 (453-540)[e]	N/A	N/A
Hospital stay (days)	12 *vs.* 6 (median)	13.2 (5-7)[e] *vs.* 6.8 (0-24)[e]	N/A	N/A
Intestinal surgery	59/108 *vs.* 56/216	25/43 *vs.* 140/592	25/43 *vs.* 46/212	108/292 *vs.* 213/1120
Mortality	PFS(mo): 20.8 *vs.* 32.7	0/43 *vs.* 3/592	30-d mortality: 1 *vs.* 1	Inpatient:
N(%)	OS(mo): 27.3 *vs.* 57.9		OS (mo): 34 *vs.* 44.8	19/292 *vs.* 15/1120

ICU: Intensive care unit; RS: retrospective; PDS: primary debulking surgery; OC: ovarian cancer; PFS: progression-free survival; OS: overall survival. [a]Mean±SD; [b]Mean (range); [c]Median (IQR); [d]Mean; [e]95%CI.

Predictors of length of ICU stay. Three studies, which included 1194 patients evaluated perioperative predictors of length of stay to various types of CCUs (11, 13, 15). Table II presents the main study and patient characteristics of the aforementioned studies. Among them, two compared 893 patients who stayed to ICU or HDU for 24 h or less *versus* 206 who required longer stay whereas the other study evaluated 41 *versus* 54 patients with <48 h *versus* ≥48 h ICU stay, respectively. The most common indication for surgery was ovarian cancer in 45% of cases. Thomakos *et al.* and Diaz-Montes *et al.* have reported that older patients required longer ICU stay (>24 h and ≥48 h, respectively) (11, 13) whereas no difference was found by Amir *et al.* (15). Thomakos *et al.* and Diaz-Montes *et al.* have reported that prolonged operative time was associated with longer ICU stay (11, 13), whereas Thomakos *et al.* and Amir *et al.* have found significantly prolonged stay in patients with higher estimated blood loss (EBL) (11, 15). Additionally, multivariate analysis by Thomakos *et al.* confirmed the aforementioned outcome concerning EBL (OR=1.13,

Table II. *Study and characteristics of women admitted postoperatively to CCUs according to length of CCU stay.*

Year; Author	2014; Thomakos	2007; Diaz-Montes	1997; Amir
Type of study	RS	RS	RS
Inclusion criteria	Surgery for gynaecological malignancies; immediate admission after surgery	OC; immediate admission after surgery	Stage III-IV OC; debulking surgery; immediate admission after surgery
Type of malignancy	OC, endometrial cancer; uterine sarcomas; vulvar cancer; vaginal cancer; fallopian cancer; cervical cancer	OC	Primary OC; Recurrent OC
Compared groups (length of CCU stay)	≤24 h *vs*. >24 h	<48 h *vs*. ≥48 h	24 h *vs*. >24 h
Indication for ICU admission	Hemodynamic monitoring: 380 *vs*. 57; respiratory disease: 30 *vs*. 10; cardiovascular disease: 366 *vs*. 97; metabolic disorder: 40 *vs*. 3; neurological disorder: 13 *vs*. 2; renal insufficiency: 11 *vs*. 5	Postoperative monitoring (main)	N/A
Patient No	840 *vs*. 174	41 *vs*. 54	53 *vs*. 32
Age (years)	60.8±15.4[a] *vs*. 64.5±14.6[a]	58.5 (22-81)[b] *vs*. 64 (36-85)[b]	63.6±12[a] *vs*. 66.9±11.8a
Charlson comorbidity index (CCI)	N/A	3.2 (1-7)[b] *vs*. 4.3 (2-10)[b]	N/A
Operative time (min)	158.2±42.2[a] *vs*. 168.8±46.6[a]	234 (81-581)[b] *vs*. 290 (76-653)[b]	190±120[a] *vs*. 225±92[a]
Blood loss (ml)	1090.4±678.1[a] *vs*. 1763.8±862.1[a]	591 (200-3000)[b] *vs*. 871 (0-3300)[b]	604±554[a] *vs*. 989±818[a]
Hospital stay (days)	N/A	10 (3-37)[c]	N/A
Intestinal resection	39/840 *vs*. 28/174	17/40 *vs*. 32/53	12/53 *vs*. 14/32
Mortality N (%)	N/A	0 *vs*. 5	N/A

CCU: Critical care units; RS: retrospective; OC: ovarian cancer; [a]Mean (SD); [b]Mean (range); [c]Median (range).

95%CI=1.10-1.16, $p<0.001$) (11). Bowel resection was presented as a significant predictor of prolonged ICU stay in uni-and multi-variate analysis by all studies except from one in which no significant difference was detected ($p=0.09$) (13). Other factors significantly associated with prolonged ICU stay were the need of >5 liters of crystalloid fluids and albumin levels <3.5 g/dl as revealed in multivariate analysis by Diaz-Montes *et al*. (13).

Discussion

The present study indicates that hemodynamic instability and fluid management were the most common indications for CCUs admission. Meanwhile age, CCI score, operative times, blood loss, intestinal resection, readmissions to hospital and survival rates played a significant role in admission to CCUs after gynecologic oncology surgical procedures. Additionally, age of patients, operative times, blood loos and any kind of intestinal resection were also significant indicators of prolonged stay to CCUs.

Postoperative admission to CCUs, following surgery in high-risk patients, intents to reduce postoperative morbidity and mortality. The decision of postoperative admission to CCUs is driven by both the patients' medical history and characteristics as well as the type and extent of surgery. To date, the available data regarding the exact proportion of patients admitted to ICU following a gynecologic oncology surgery is limited. According to the study by Kumar *et al*., all obstetrical and gynecological procedures represented a proportion of 13% of all postoperative ICU admissions with concurrent grastrointestinal surgery being the most prevalent indication with 28% (22). Nonetheless, no separate data concerning gynecologic oncology patients was available in this study.

According to the findings of the present study, the majority of admissions to the ICU were noted in ovarian cancer patients and patients with advanced stage disease. This is in accordance with the complexity of the debulking procedures that patients with disseminated ovarian cancer require in order to achieve complete cytoreduction, which is considered the main target in these patients so as to improve their survival (23). In that setting, our study shows that concurrent intestinal resection of any kind as part of cytoreductive gynaecological surgery was a critical predictor

of admission to CCUs. This can be explained by the increased risk of severe postoperative complications that have been reported in patients who underwent rectosigmoid surgery as a part of pelvic exenteration (24). Additionally, concurrent performance of intestinal resections may result in protracted operative time, considered an independent predictor of postoperative ICU admission.

The effect of NACT on postoperative admission to ICU following gynaecologic surgery is also controversial. Patients with advanced stage disease considered unresectable at initial assessment have been shown to benefit significantly from NACT followed by interval debulking surgery (IDS) and adjuvant chemotherapy (25). Several recent studies have reported increased rates of complete cytoreduction along with significantly decreased perioperative morbidity and mortality in patients who had IDS compared to those having primary debulking procedures for advanced stage ovarian cancer (26). This can be probably attributed to the critical reduction in the extent of the disease due to NACT and the respective requirement of less complex procedures. Consequently, a respective decline in the rates of postoperative ICU admission is theoretically expected. Pepin *et al*. have noted that patients who received NACT were less likely to be admitted to the ICU post-IDS when compared to primary debulking surgery (PDS) (10). On the other hand, according to the outcomes derived from a small part of patients from the population study by Ross *et al*., NACT was not an indicator of ICU admission while suboptimal cytoreduction was significantly associated with unplanned ICU admission (9).

The present study indicated a prolonged CCU stay in patients of older age, with longer operative times, higher blood loss rates as well as those who had concomitant intestinal resection, higher needs of fluid replacement and those with low albumin levels. The role of preoperative nutritional status as a predictor of the postoperative course of patients undergoing gynaecological procedures has been also investigated. To that end, Kathiresan *et al*. have reported significantly increased ICU admissions in patients with preoperative albumin levels of 3.9 g/dl or less (18).

A variety of scoring systems such as the American Society of Anesthesiologists physical status (ASA), acute physiology and chronic health evaluation (APACHE), specified acute physiology score (SAPS), estimation of physiological ability and surgical stress (E-PASS) and national surgical quality improvement program (NSQIP), have been recommended so as to designate critically ill surgical patients who will require more intensive postoperative care in respective units as well as to predict the postoperative course of patients admitted to CCUs (27). More specifically, the APACHE score system was firstly introduced in 1981 and was consisted by two parts evaluating aspects of the patients' current illness as well as the patients performance status and co-morbidities before admission so as to effectively manage patients after various surgeries (28). Elevated APACHE scores have been correlated to increased postoperative mortality and adverse outcomes in patients admitted to ICU. regarding the gynecologic oncology patients admitted to ICU who were evaluated according to the second revision of APACHE score (APACHE II) and found to have scores ≥20 were at approximately 80% risk of postoperative mortality(20). Accordingly, Leath *et al*. have noted significantly elevated mean APACHE II scores in surgically managed gynecologic patients admitted to the ICU and died during the postoperative course compared to surviving ones (21. *versus* 11.5, $p<0.001$) (19). Additionally, another scoring system evaluating preoperatively the impact of comorbidities of critically ill patients on survival and prognosis is the CCI scoring system (29). Three of the included studies in the present analysis presented outcomes with regards to CCI scores of recruited patients (10, 12, 14). Among these, two detected a significant association between elevated CCI scores and admission to the ICU (12, 14). This not only highlights the importance of preoperative evaluation of comorbidities of patients but also pinpoints the significant their role in the postoperative course. While the majority of available scoring systems evaluate patients according to their past medical history and performance status, they do not consider the impact of some surgical outcomes. Intraoperative outcomes have also been considered of critical importance for predicting admission to the ICU and prolonged stay in the respective units. In particular, we observed that gynecological patients who underwent prolonged surgery and had high blood loss were more likely to be postoperatively transferred to CCUs. Subsequently, the fact that blood loss was a significant indicator of admission to the CCU could probably explain why hemodynamic instability and fluid management were the most common indications of admission. Comparable outcomes regarding the effect of operative times and blood loss have been observed in other surgical procedures such as restoration of lumbar spine diseases (30). Meanwhile, management of hemodynamic status of patients has been acknowledged as a key factor to decrease postoperative mortality (31).

In the present study, a meticulous review of the current literature was performed. Data restrictions were avoided with the intent to eliminate data losses, which consists a significant strength of our study. To the best of our knowledge, this is the first review assessing the clinical significance of patients who underwent gynecologic oncology. However, reaching conclusions, a number of limitations should be taken into account. In that setting, the lack of long-term survival outcomes by the majority of the included studies constitutes a significant limitation. More specifically, only Ruskin *et al*. have presented a 30-day mortality of 2.3% in ICU patients while the respective rate in the literature ranges from approximately 11% to 28% (12).

Furthermore, the significant discrepancy among the included studies with regards to the type, structure and definition of intensive care units further precludes extraction of cumulative outcomes.

The selection of patients that require monitoring in CCUs and will benefit from admission still remains equivocal and requires multidisciplinary approach by gynaecological oncologists, anaesthesiologists and intensive care physicians. The appropriate preoperative assessment of patient's condition and disease severity, will enable gynecologic oncologists to successfully perform major gynecologic procedures with favourable short- and long-term operative outcomes. Further prospective studies in the field with final aim the establishment of respective protocols will allow gynecologic oncologists to properly identify patients in need of postoperative CCU admission and will ensure resource utilization and cost-effectiveness. Furthermore, the recent introduction of enhanced recovery after surgery (ERAS) programs in gynecologic oncology seem promising in achieving a fast functional recovery of patients, improved postoperative outcomes along with cost-effectiveness (32). As far as the responsibilities of gynecologic oncologists is concerned, preoperatively, a consistent assessment of the extend of the disease and a thorough planning of the required surgical procedures on the basis of the patient's co-morbidities and performance status are paramount. Moreover, postoperatively, the gynecologic oncologist is the practitioner who is mainly responsible for the daily monitoring of the patient and for making the final decisions with regards to the patient's course as knowing the exact patients' condition along with the performed operative procedure (5). Consequently, we strongly advocate the incorporation of rotation in CCUs in gynecologic oncology fellowship programs aiming at efficiently managing these patients and improve their quality of life and survival. To that end, fellows will be trained in the field including fluid management, pain control and sepsis treatment and will thus gain experience in the postoperative management of critically severe cases.

Conclusion

Demographic aspects of patients who underwent gynecologic oncology procedures such as age as well as intraoperative outcomes such as operative times, blood loss and intestinal surgery are predictive of CCU admission and length of CCU stay. Further larger prospective studies are needed to designate high-risk patients who will benefit from postoperative care in CCUs with the intent to avoid unnecessary admissions and waste of institution's resources while simultaneously ensure favorable postoperative outcomes. It is the responsibility of the gynecologic oncologist to provide extensive preoperative patient counseling with special consideration on the need of individualization.

Conflicts of Interest

The Authors have no conflicts to disclose in relation to this study.

Authors' Contributions

NT had the initial idea for the project, developed the project, wrote the manuscript and provided consultation, AP developed the project, collect the data and was a major contributor in writing the manuscript, DH provided consultation to the manuscript, NM collected the data and wrote the manuscript and AR provided consultation to the manuscript and supervised the project. All Authors read and approved the final manuscript.

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