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Clinical-Bladder cancer

Factors influencing ICU admission and associated outcome in patients undergoing radical cystectomy with enhanced recovery pathway

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Abstract

Purpose: To characterize drivers of ICU admission during index hospitalization after Radical Cystectomy (RC) with Enhanced Recovery After Surgery (ERAS) protocol, as well as corresponding outcomes.

Methods: A retrospective review of an IRB-approved cystectomy database was conducted. All patients who underwent RC with ERAS protocol from 2012 to 2017 were included. Exclusion criteria: adjunct nephrectomy or urethrectomy.

Results: A total of 512 patients were identified. ICU admission in index hospitalization was reported in 33 patients (6.4%), 26 with unplanned ICU transfer after initial non-ICU level of care and 7 with planned direct postoperative ICU admission. Higher age and Charlson Comorbidity Index ≥3 were significant risk factors for unplanned ICU admission. On multivariate analysis, age remained associated (odds ratio 1.05, 95% confidence interval 1.008, 1.1, $P = 0.02$) and Charlson Comorbidity Index ≥3 kept the trend (odds ratio 2.16, 95% confidence interval 0.86 − 5.07, $P = 0.08$) with this increased risk of ICU admission. Patients in the unplanned ICU group spent a median of 3 days (range: 0−32) at non-ICU level of care before ICU transfer; cardiac indications were the most common reason for transfer (52%). Patients who required unplanned ICU transfer had a median length of stay of 11.5 days, compared to a length of stay of 5 days ($P < 0.01$) for non-ICU patients. Ninety-day readmission and mortality rates were higher in the planned ICU cohort when compared to the unplanned ICU cohort. A low rate of ICU admission (2.7%) in the corresponding 90-day postoperative period was reported for the group not requiring ICU admission during index hospitalization.

Conclusion: ICU admission is uncommon following RC with ERAS protocol. Advanced age and comorbidity index are significantly associated with unplanned ICU transfer. Planned ICU admissions are not shown to be associated with improved outcomes compared to unplanned ICU admissions. Further efforts to elucidate the role of ICU care in the context of the ERAS protocol is important for targeted care optimization and appropriate postoperative planning.

Keywords: ERAS; ICU admission; Radical cystectomy; Bladder cancer; Outcome

1. Introduction

The enhanced recovery after surgery (ERAS) protocol was first developed to optimize perioperative management of patients undergoing colorectal surgery. The main focus was to decrease length of stay without increasing complication and readmission rates [1−3]. Since its creation, the ERAS protocol has been adopted for other surgeries, including radical cystectomy (RC), which remains the standard treatment for muscle invasive bladder cancer [2,4−6].

Our institution adopted the ERAS protocol for RC in 2012, and reported a reduced length of stay with no increase in 30-day readmission rates [7]. A follow-up evaluation reported infections as the most common cause of 90-day complications, readmissions, and ER visits [8]. To further investigate and optimize the safety of this protocol, we

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evaluated the postoperative course of these patients during index hospitalization. With the ERAS protocol, RC patients are transferred to non-ICU level care after surgery. In fact, some studies prior to the ERAS era have reported that mandated ICU admission following RC is not required [9,10]. However, high-grade complications may require patient transfer from non-ICU to ICU level of care before date of discharge. In addition, some patients with more advanced comorbidities or intraoperative complications continue to undergo planned direct postoperative ICU admission without initial non-ICU level of care. Currently, ICU admissions in the setting of ERAS protocols, regardless of timing and indication, have not been adequately investigated.

The objective of this study is to explore possible risk factors associated with unplanned ICU admissions. We also report corresponding outcomes for all patients in our study to better evaluate the role of ICU management after RC in the contemporary ERAS era.

2. Materials and methods

2.1. Study population

All consecutive patients (541) who underwent RC with intent to cure under the ERAS protocol at our institution from 2012 to 2017 were reviewed for inclusion in this study using an IRB-approved bladder cancer database. A total of 29 patients with adjunctive procedures (nephrectomy and urethrectomy) were excluded. The remaining 512 patients were then further evaluated for ICU admission during index hospitalization, and 33 such patients were identified. Patients were divided into 3 groups using this parameter: (1) no ICU admission in index hospitalization, (2) unplanned ICU transfer from non-ICU level of care in index hospitalization, and (3) planned direct postoperative ICU transfer without first receiving non-ICU level of care. Refer to Appendix 1 for our institutional ERAS protocol and Appendix 2 for telemetry and ICU capabilities at our institution.

Of note, direct comparison between group 1 and group 3 was not performed because the latter cohort undergoes perioperative planning for direct ICU admission. While these patients remain on the ERAS protocol, they have predetermined deviations from the normal pathway of non-ICU postoperative management. Consequently, these ICU admissions are planned and are not directly associated with modifiable postoperative risk factors. As such, the decision was made not to include these patients in the analysis for factors influencing unplanned ICU transfers. The inclusion of group 3 in this study serves to help examine the role of planned ICU management in ERAS protocols by allowing for comparison between planned and unplanned ICU admissions.

2.2. Data collection and analysis

Our prospectively maintained, IRB-approved bladder cancer database was reviewed retrospectively for the 512 patients included in this study. Patient demographics, operative variables, and 90-day postoperative outcomes were collated. Charlson Comorbidity Index (CCI) is reported as a categorical variable (<3 and ≥3). Postoperative complications are reported using the Clavien-Dindo classification system: grade 1, 2 are grouped as "low grade", and grade 3, 4, 5 are grouped as "high grade." By definition, at least 1 high grade (grade 4+) complication was recorded for the patients in the unplanned ICU-admission cohort. Therefore, comparisons involving the unplanned ICU cohort were made across low grade and grade 3 complications. Of note, some patients in the planned ICU cohort were admitted to the ICU for close observation rather than recorded high-grade complications.

To evaluate all ICU admissions in more detail, patients in both ICU cohorts were further categorized based on indications for ICU transfer. A deeper dive analysis was performed on the perioperative period leading to ICU transfer as well as outcomes after return to regular ward. Perioperative and outcome variables were compared between groups 2 and 3 to investigate the differences between planned vs. unplanned ICU admissions.

Statistical analysis was done to compare variables between cohorts. All variables, including ICU-related measures, were compared among the different indications of ICU admission. Statistical software package SAS, Version 9.4 (SAS Institute Inc., Cary, NC) was used for all the analyses in this study. Pearson's chi-square or Fisher's exact tests were used to examine the association between categorical demographic and clinical variables, and Kruskal Wallis tests to examine the differences in not normally distributed continuous variables. Finally, for the comparison between group 1 and group 2, stepwise multivariable logistic regressions were performed to model the ICU rate with putative demographic and clinical predictors. All P-values reported are 2-sided and $P < 0.05$ is considered statistically significant.

3. Results

A total of 512 patients underwent RC with intent to cure with our perioperative ERAS protocol during the defined period. During index hospitalization, 479 patients (94%) were not transferred to the ICU while 26 patients (5%) were transferred from initial non-ICU level of care to the ICU and 7 patients (1%) were admitted to ICU directly from the operating room. These 3 cohorts correspond to groups 1, 2, and 3, respectively. Patient demographics and postoperative variables for all cohorts are summarized in Tables 1 and 2.

3.1. Factors influencing unplanned ICU admissions

Direct comparison between groups 1 and 2 was performed. Patients in group 2 had a higher median age and proportion of patients with CCI ≥ 3 ($P = 0.004$, $P = 0.01$,

Table 1
Demographic and perioperative variables

Demographics						
Variables		No ICU admission	ICU transfer	Direct ICU admission	*P* values (1v2)	*P* values (2v3)
Number of patients		479	26	7		
Age	Median (range)	70.7 (34.9−92.0)	79 (48−88)	76 (64−82)	0.004	0.9
Gender	Male (%)	409 (85)	24 (92)	5 (71)	0.3	0.1
Race	Caucasian (%)	432 (90)	23 (88)	6 (86)	0.8	0.5
	African American (%)	10 (2)	1 (4)	1 (14)		
	Asian (%)	37 (8)	2 (8)	0		
BMI	Median (range)	27.07(16.53−44.52)	26.61 (15.96−36.92)	22.79 (21.08−37.09)	0.4	0.5
CCI (sum)	≥3 (%)	75 (16)	9 (35)	2 (29)	0.01	0.8
Significant CCI categories	MI (%)	28 (6)	5 (19)	1 (14)	<0.01	0.8
	CHF (%)	11 (2)	3 (12)	0	<0.01	0.3
Neoadjuvant chemotherapy (%)		149 (31)	7 (27)	1 (14)	0.6	0.5
Neoadjuvant radiation (%)		13 (3)	1 (4)	0	0.7	0.6
Past abdominal surgery (%)		149 (31)	12 (46)	4 (57)	0.1	0.6
Surgical approach	Open (%)	339 (71)	20 (77)	4 (57)	0.5	0.3
	MIS (%)	140 (29)	6 (23)	3 (43)		
OR time (min)	Median (range)	350 (173−695)	347.5 (230−652)	436 (237−564)	0.7	0.3
EBL (cc)	Median (range)	350 (30−2500)	325 (100−1000)	500 (75−10500)	0.1	0.0513
Diversion type	Orthotopic (%)	280 (58)	13 (50)	2 (29)	0.3	0.3
	Heterotopic (%)	199 (42)	13 (50)	5 (71)		
Path stage (T)	>pT2 (%)	140 (29)	6 (23)	4 (57)	0.5	0.08
Path stage (N)	N+ (%)	91 (19)	4 (15)	2 (29)	0.6	0.4
Path stage (M)	M+	0	0	0	-	-
Intraoperative complication (%)		15 (3)	2 (8)	2 (29)	0.2	0.1
Perioperative transfusion (%)		133 (28)	13 (50)	5 (71)	0.015	0.3

respectively). Closer inspection of the CCI categories revealed significantly higher proportions of past myocardial infarctions and congestive heart failure in this unplanned ICU cohort ($P = 0.007$, $P = 0.005$, respectively). On multivariate analysis controlling for age and CCI, CCI ≥ 3 kept the trend (odds ratio 2.16, 95% confidence interval 0.86 − 5.07, $P = 0.08$) while age remained significantly associated (odds ratio 1.05, 95% confidence interval 1.008 − 1.1, $P = 0.02$) with an increased risk of ICU admission (Table 4). A longer median LOS of 11.5 days during index hospitalization was reported in group 2 compared to 5 days for the group 1 ($P < 0.01$). However, intraoperative complication as well as 90-day complication and readmission rates were not significantly different. Perioperative blood transfusion was also reviewed as a comparison variable, and occurred nearly twice as frequently in the unplanned ICU cohort as

Table 2
Postoperative variables

Postoperative						
Variables		No ICU admission	ICU transfer	Direct ICU admission	*P* values (1v2)	*P* values (2v3)
Hospital LOS	Median (range)	5 (2−23)[a]	11.5 (4−43)[b]	5 (3−29)[c]	<0.01	0.1
90-day complications	Any complication (%)	360 (75)	26 (100)	7 (100)	**	-
	Low grade* (%)	343 (72)	23 (88)	5 (71)	0.06	0.3
	High grade* (%)	80 (17)	26 (100)	4 (57)	**	**
	Grade 3 (%)	68 (14)	4 (15)	3 (43)	0.8	0.1
	Grade 4 (%)	13 (3)	25 (96)	2 (29)	**	**
	Grade 5 (%)	8 (2)	1 (4)	3 (43)	0.4	<0.01
90-day readmissions (%)		157 (33)	8 (31)	6 (86)	0.8	<0.01
Follow-up (mo)	Median (range)	10.2 (0.26−50.7)	12.9 (1.3−47.5)	5.5 (0.1−38.0)	0.2	0.2
Disease recurrence (%)		86 (18)	4 (15)	0	0.7	0.3

Outliers:
[a] LOS 23 days: partial SBO requiring partial parenteral nutrition and subsequently developed UTI with leukocytosis.
[b] LOS 43 days: rectotomy requiring revision surgery.
[c] LOS 29 days: right lower extremity thrombosis requiring revision surgery.
* Low Grade = Clavien 1, 2. High Grade = Clavien 3, 4, 5.
** By definition, ICU cohorts have higher complication rate (100%) and more grade 4+ complications. (admits to ICU).

compared to the non-ICU cohort (50% vs. 27.8%, $P = 0.001$). Although this difference was significant, only 2 patients in the unplanned ICU cohort (7.7%) received transfusions before ICU admission. Following ICU transfer, 13 patients in this cohort, including the 2 patients that received pre-ICU transfusions, had recorded transfusions. After a median follow-up of 10.3 months (range 0.26−50.7) for patients in both above cohorts, disease recurrence rate was not significantly different.

3.2. Planned vs. unplanned ICU admissions

A total of 33 patients in our study received ICU level of care during index hospitalization (6.4%). These patients correspond to group 2 (unplanned ICU admissions) and group 3 (planned ICU admissions).

Demographic and perioperative characteristics were not significantly different between these 2 cohorts. The postoperative course of the 2 cohorts was also not significantly different in terms of LOS and 90-day complication rates. However, higher 90-day mortality and readmission rates were observed in group 3 ($P < 0.01$, $P < 0.01$, respectively). After a median follow-up of 10.8 months (range: 0.1 −47.5), disease recurrence was not significantly different.

ICU-specific variables are delineated in Table 3. During index hospitalization, 23 patients in group 2 (88%) had 1 ICU admission and 3 patients (12%) had 2 admissions. Cardiac indications were the most common cause of ICU admission in this group (52% of admissions). Patients in this cohort remained on non-ICU level of care for a median of 3 days (range: 0−32) before transfer to the ICU. For group 3, the indications for planned postoperative ICU transfer were complicated comorbidities for 5 patients (71%) and intraoperative complications for 2 patients (29%). The median ICU LOS in index hospitalization was not significantly different between groups 2 and 3.

Table 4
Multivariate logistic regression of risk factors for ICU admission in index hospitalization

Variables	Odds ratio (95% CI)	*P* value
Age	1.054 (1.008, 1.105)	0.024
CCI ≥ 2	2.162 (0.869, 5.073)	0.083

4. Discussion

Existing literature on the ERAS protocol for RC reports decreases in length of stay with no increase in complication and readmission rates. Studies have evaluated the effects of adopting ERAS protocol at different institutions and reported improved outcomes in terms of intraoperative blood loss, transfusion rates, return of bowel function, and incidence of postoperative ileus [6,7,11−17]. The accelerated rate of recovery and reduced length of stay associated with ERAS protocol makes it the most ideal pathway currently available in terms of cost, outcome, and overall patient care.

However, less literature has investigated specific aspects of the ERAS pathway that may serve as targets for further optimization. In particular, factors leading to ICU admission (high-grade complications) following RC with adherence to the ERAS protocol and corresponding outcomes have not been well studied. A few studies that allude to such ICU events have found no significant variables associated to these events; most report reduced overall ICU length

Table 3
ICU indications and variables

ICU-specific variables						
Variables		ICU transfer		Direct ICU admission		*P* values
Primary reason for ICU admission/transfer		Cardiac[a]	15	Complicated PMH[d]	5	
		Infectious[b]	4			
		Vascular	3	Intraoperative complication[e]	2	
		Other[c]	7			
Days of non-ICU level of care before ICU transfer	Median (range)	3 (0−32)[f]		-		
ICU LOS	Median (range)	3 (1−18)[f]		2 (2−3)		0.2

Outliers:

Days of non-ICU level of care before ICU transfer 32 days: long hospital course with wound dihescence requiring revision surgery that was complicated by prolonged intubation and infection.

ICU LOS 18 days: rectotomy requiring revision surgery − total LOS 43 days.

[a] Most common cardiac etiologies in order of descending frequency: atrial fibrillation, myocardial infarction, and supraventricular tachycardia.
[b] Most common infectious etiologies in order of descending frequency: aspiration pneumonia, bacteremia.
[c] Other reasons for ICU admission: GI bleed, acute renal failure, and respiratory failure.
[d] Complicated PMH include CAD, COPD, Parkinson's, and Pleural disease.
[e] The 2 reported intraoperative complications are right common femoral artery thrombus and right common iliac vein laceration.
[f] For patients with more than 1 indication for ICU transfer:

- Days on non-ICU care before transfer to ICU is calculated as days before first ICU transfer.
- ICU LOS is calculated as total ICU LOS across all indications.

of stay through implementation of enhanced recovery protocols [16,17]. Therefore, we present our experience with ICU admissions in the setting of RC with ERAS protocols to introduce a framework for evaluating these high-grade complications.

We report a low ICU admission rate of 6.4% in our cohort. Unsurprisingly, a longer LOS was reported for the unplanned ICU group compared to the non-ICU group. However, the number of 90-day low-grade complications, readmissions, oncologic outcome, and mortality rate were not affected by ICU admission during index hospitalization. In addition, the rate of ICU level readmission for patients who did not require ICU care during index hospitalization was low at 2.7% in the corresponding 90-day postoperative period. Our results suggest that ICU complications occur most commonly during index hospitalization, but once managed, outcomes are not significantly affected. Therefore, optimizing care in the time period between completion of surgery and date of discharge should be a priority.

We investigated factors associated with unplanned ICU admission after RC with ERAS protocol and found that advanced age and CCI $\geq$ 3 are correlated to an increased risk of ICU admission. Although perioperative transfusion rates were significantly higher in the ICU cohort, most of these transfusions occurred after ICU transfers and are challenging to associate with ICU admissions. It is important to note that the modifiable risk factors explored in this study, including surgical approach, estimated blood loss, pathological stage, and others listed in Table 1, were not found to be significantly associated with increased risk of ICU admission. While more modifiable risk factors remain to be evaluated, it may be important for patients with higher age and CCI to establish reasonable expectations regarding possible ICU admission in the postoperative course. However, given the wide range of ages seen in the non-ICU cohort, additional metrics such as frailty scores or other markers of overall health may be necessary to stratify patients to an appropriate pathway [18].

The benefit of lowering the threshold for planned direct postoperative ICU management for high-risk patients, i.e. advanced age and CCI $\geq$ 3, was considered. Our current data reveals higher 90-day mortality and readmission rates for the planned ICU cohort; this may be attributable to more complex comorbidities in this group, which led to perioperative concern that prompted immediate ICU level of care. Notably, there was no significant difference in ICU and total hospital LOS between the 2 ICU cohorts. While there may be possible benefits for direct ICU admission, especially in complicated cases, our results show no clear indicator for these admissions aside from intraoperative concern secondary to complicated medical history or intraoperative complications. Nonetheless, our sample size is small and further evaluation of this threshold may elucidate a clearer role for direct postoperative ICU management.

Our data on the different indications for ICU admissions highlight cardiac comorbidities as a driver for ICU admissions. Therefore, further evaluation and optimization of modifiable factors associated with cardiac conditions may reduce the incidence of ICU admission in select patients. One such variable is fluid management, which has been a focus of several studies. Una Orejon et al. evaluated the effect of an intraoperative, goal directed fluid therapy and found no significant associations with outcome for laparoscopic cystectomy [19]. Our institution reported a lack of association between intraoperative fluid intake and postoperative complications for RC [20]. Despite no evidence for a global relationship between intraoperative fluid management patterns and complications after RC, patients with predisposition to cardiac complications would represent an important subgroup in which to clarify the impact of fluid management on perioperative complications. For better or worse, our population of patients requiring ICU admission during the ERAS era was small and thus, such analysis is limited in power with our current data.

Another driver of ICU admission was infectious complications. In our study, 4 patients (15%) of the unplanned ICU cohort had high-grade infectious complications. Many studies have found infections to be the leading cause of complication and readmission in the 90-day period following RC with ERAS protocols [8,21,22]. Some studies further evaluated these postoperative infections and their treatments [23−27]. A study done at the Mayo Clinic found perioperative blood transfusion to be associated with urinary tract infections after RC and supported the use of initial broad-spectrum coverage to minimize the occurrence of these infections [24]. Liu et al. reported similar findings and advocated for the use of blood conservation strategies to minimize these complications [25]. Two other studies reported reduction in infections and readmissions after RC with the use of prophylactic antibiotics [26,27]. Currently, management of several modifiable factors, including blood transfusion and comorbidities such as diabetes, along with prophylactic antibiotic treatment guides the discussion of infection prevention following RC. Incorporating prophylactic infection protocols into the ERAS pathway may help to minimize infectious complications and in turn, enhance immediate recovery and even reduce long-term complication and readmission rates.

This study has several limitations. First is the discrepancy in number between patients with and without ICU admissions, which is largely the result of a low frequency of ICU admissions following RC with the ERAS protocol at our institution, limiting statistical analysis. Secondly, adherence to the ERAS protocol is difficult to assess for patients who develop high-grade complications and deviate from the ERAS pathway. However, it should be noted that ERAS adherence in our control group is satisfactory without significant deviations. Another limitation is the inherent subjectivity in threshold for ICU admissions as there is variability among providers and institutions. Lastly, the results reported are from a single, high-volume academic center and external validation from a variety of institutions with standardized ERAS protocols is required.

Future efforts to reduce ICU admissions should focus on exploring modifiable factors including perioperative fluid management, transfusions, and infection control, especially in the postoperative period of index hospitalization. Evaluating the role of planned postoperative ICU management in select patients for whom ICU care may be unavoidable is also important. Better stratification of patients by utilizing more accurate markers of overall health, such as frailty scores and sarcopenic measures, may help to expand our current rudimentary risk factors of advanced age and CCI.

5. Conclusion

ICU admission during index hospitalization is uncommon following modern RC with adherence to the enhanced recovery protocol. Advanced age and high CCI, especially with the presence of cardiac comorbidities, are potential risk factors for unplanned ICU transfer. Planned ICU admissions are not shown to be associated with improved outcomes when compared to unplanned ICU admissions and both are associated with lengthy hospital stay. Further efforts to elucidate the role of ICU care in the context of the ERAS protocol is important for targeted care optimization and appropriate postoperative planning.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.06.019.

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