Structured Multidisciplinary Approach to Ruptured Abdominal Aortic Aneurysm: Impact on Mortality and Complications in a 13-Year Cohort

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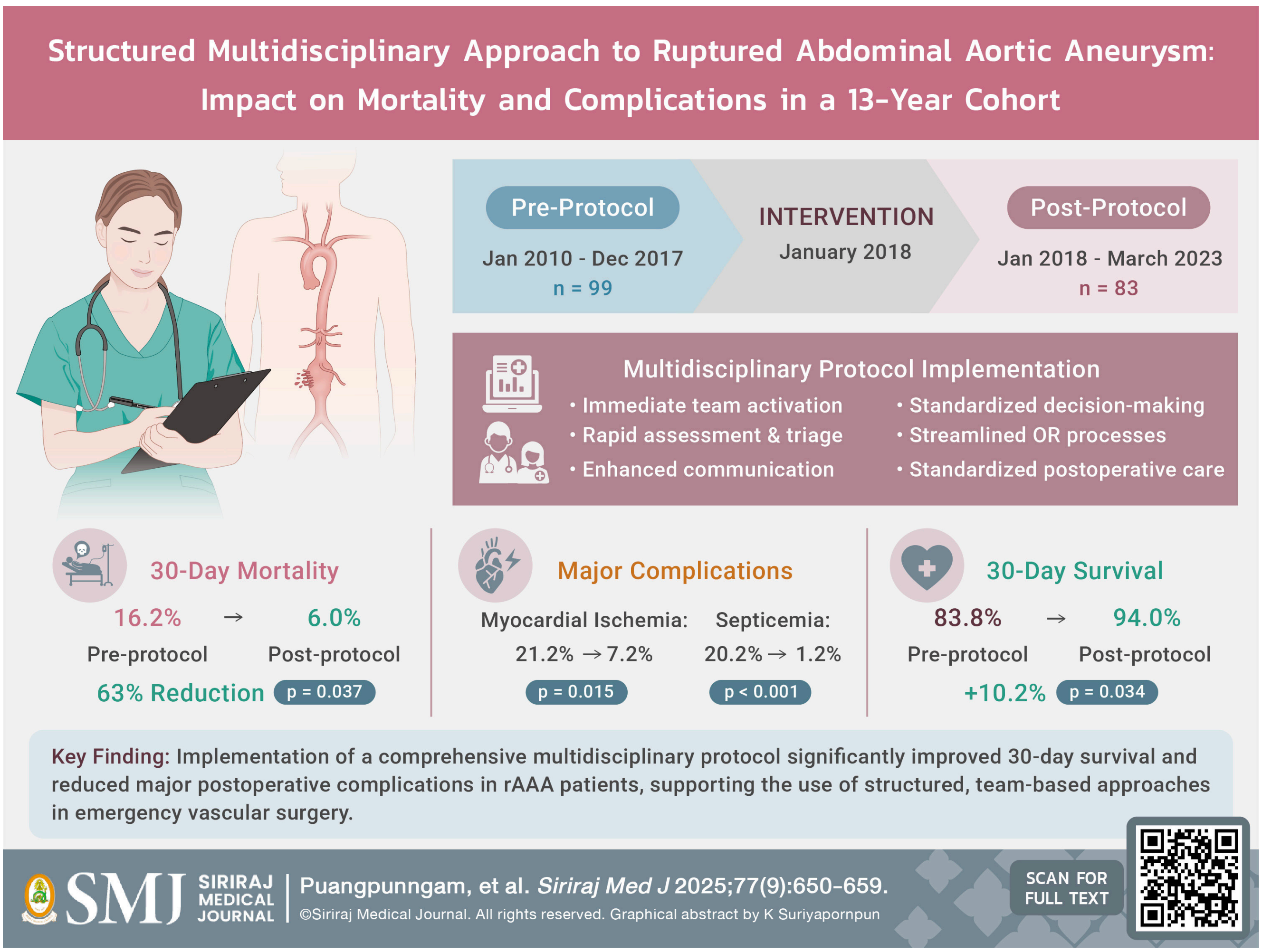

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ABSTRACT

Objective: To evaluate the impact of a comprehensive multidisciplinary protocol on 30-day survival in ruptured abdominal aortic aneurysm (rAAA) patients and to identify factors influencing outcomes.

Materials and Methods: We conducted a retrospective study comparing outcomes before and after implementation of a multidisciplinary protocol for rAAA management at Siriraj Hospital. The study included 182 patients (pre-protocol: n=99, January 2010-December 2017; post-protocol: n=83, January 2018-March 2023). Primary outcome was 30-day overall survival, with secondary outcomes including factors influencing survival, need for aortic balloon occlusion, operative parameters, length of stay, and complications.

Results: The 30-day mortality rate significantly decreased from 16.2% pre-protocol to 6.0% post-protocol (p=0.037). Kaplan-Meier analysis showed improved 30-day survival in the post-protocol group (94.0% vs 83.8%, p=0.034). However, while protocol implementation was associated with a non-significant reduction in mortality hazard (adjusted HR 0.509, 95% CI 0.175-1.478, p=0.213), multivariable analysis identified cardiac arrest (aHR 8.180, p<0.001) and unfit patient status (aHR 6.420, p=0.003) as independent predictors of mortality. The post-protocol group had significantly reduced myocardial ischemia (7.2% vs 21.2%, p=0.015) and septicemia (1.2% vs 20.2%, p<0.001), with no significant differences in operative parameters or length of stay.

Conclusion: Implementation of a multidisciplinary protocol for rAAA management was associated with improved 30-day survival and reduced postoperative complications, supporting the use of structured protocols in rAAA management.

Keywords: Ruptured AAA; protocol; multidisciplinary team; outcomes; perioperative mortality (Siriraj Med J 2025; 77: 650-659)

INTRODUCTION

Ruptured abdominal aortic aneurysm (rAAA) represents one of the most critical emergencies in vascular surgery, requiring immediate medical attention and surgical intervention.[1] It remains a life-threatening condition associated with high mortality rates, with recent studies reporting mortality rates ranging from 30% to 50%.[2,3] Despite advancements in surgical techniques and perioperative care, the management of rAAA continues to pose significant challenges to healthcare providers. The time-sensitive nature of the condition, coupled with the complex interplay of factors affecting patient outcomes, necessitates a coordinated and efficient approach to care.[4]

In recent years, there has been growing interest in the implementation of standardized protocols and multidisciplinary approaches to improve outcomes in rAAA patients.[5,6] These protocols aim to streamline the diagnostic and treatment processes, optimize resource utilization, and enhance communication among various healthcare team members involved in patient care.

Our institution, Siriraj Hospital in Bangkok, Thailand, implemented a comprehensive multidisciplinary protocol for rAAA management in January 2018. This study aims to evaluate the impact of this protocol on 30-day overall survival in rAAA patients and identify factors influencing outcomes. By comparing pre- and post-protocol periods, we seek to provide valuable insights into the effectiveness of structured approaches in managing this critical condition.[7] However, our outcomes could have been influenced by several confounding factors that evolved over time, including advancements in device technologies, improved ICU care, and increased surgeon experience.

The findings of this study have the potential to inform clinical practice and contribute to the ongoing efforts to reduce mortality and morbidity associated with rAAA.[8] Moreover, by identifying predictors of mortality, we aim to enhance risk stratification and guide decision-making in the acute management of rAAA patients.[9]

MATERIALS AND METHODS

Study design and population

We conducted a retrospective study at Siriraj Hospital, a tertiary referral center in Bangkok, Thailand, comparing outcomes before and after implementation of a multidisciplinary protocol for rAAA management. The study included all patients treated for rAAA between January 2010 and March 2023, divided into pre-protocol (January 2010-December 2017) and post-protocol (January 2018-March 2023) groups.

Inclusion and exclusion criteria

The study included patients with radiologically or intraoperatively confirmed rAAA who were aged ≥ 18 years, who underwent either endovascular aortic aneurysm repair (EVAR) or open surgical repair (OSR). We excluded patients who died before surgical intervention, those with thoracoabdominal aortic aneurysms, and individuals with previous aortic surgery. The Siriraj Institutional Review Board (SIRB) granted ethical approval for this research investigation under certificate of approval number Si 279/2022.

Multidisciplinary protocol

In January 2018, we implemented a comprehensive multidisciplinary protocol with several key components (Fig 1). The protocol mandated immediate activation of a multidisciplinary team upon suspicion of rAAA, followed by rapid assessment and triage based on hemodynamic stability. For stable patients, we conducted expedited computed tomography angiography (CTA). The protocol established a standardized decision-making process for EVAR versus OSR and included preparation for potential aortic balloon occlusion in unstable patients. We activated a massive transfusion protocol when necessary and streamlined transfer processes for patients from referring hospitals. The protocol also ensured dedicated operating room availability for rAAA cases, preparedness for aortic balloon occlusion, standardized postoperative care, and regular team training and simulation exercises.

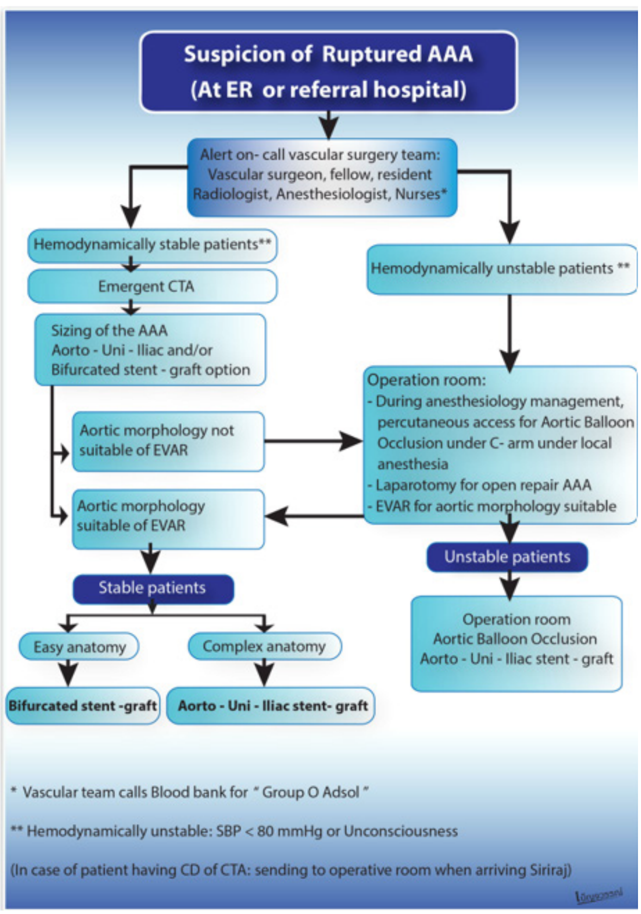

Fig 1. Multidisciplinary approach in managing ruptured abdominal aortic aneurysms.

Data collection

We collected data on patient demographics, comorbidities, preoperative condition, intraoperative details, and postoperative outcomes. Preoperative variables included age, gender, comorbidities (hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, and renal insufficiency), fit status, hemodynamic condition, and laboratory values. Impaired kidney function was characterized by serum creatinine exceeding 2 mg/dl. Patient classification as fit or unfit for intervention followed criteria established in the United Kingdom's EVAR 1 and 2 clinical trials, which evaluated patients based on cardiovascular, pulmonary, and kidney function parameters.[10] Intraoperative data encompassed the type of repair (EVAR or OSR), operative time, estimated blood loss, and use of aortic balloon occlusion. Postoperative variables included length of intensive care unit (ICU) and hospital stay, complications, and 30-day mortality.

Outcomes measurement

The primary outcome was 30-day overall survival. Secondary outcomes included factors influencing survival, need for aortic balloon occlusion, operative time, blood loss, length of hospital and ICU stay, and postoperative complications (including myocardial infarction, respiratory failure, renal failure requiring dialysis, bowel ischemia, and sepsis).

Statistical analysis

For statistical analysis, we employed various methods to compare the two groups and assess factors associated with 30-day survival. For categorical data, we used Pearson chi-square test, Yates' continuity correction, or Fisher's exact test as appropriate. Continuous data were analyzed using independent t-tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. We utilized the Kaplan-Meier method to generate survival curves and calculate survival rates, with differences between groups assessed using the log-rank test. To identify factors associated with 30-day survival, univariable logistic regression analyses were performed to identified potential predictors. Variables with p-values < 0.1 in the univariable analysis were subsequently entered into a multivariable logistic regression model using the backward stepwise selection method based on the likelihood ratio test (SPSS, PIN = 0.05, POUT = 0.10). Associations were quantified using both unadjusted and adjusted hazard ratios (HR) with corresponding 95% confidence intervals (95% CI). All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The study comprised 182 patients with ruptured abdominal aortic aneurysm (rAAA), who were divided into two cohorts based on treatment protocol implementation: a pre-protocol group (n=99; endovascular aortic repair [EVAR] n=72, open surgical repair [OSR] n=27) and a post-protocol group (n=83; EVAR n=44, OSR n=39). (Fig 2).

Demographic and clinical characteristics

The mean age of the study population was 72.3 ± 10.7 years, and 84.1% were male. Hypertension was the most common comorbidity (74.7%), followed by dyslipidemia (30.2%) and renal insufficiency (22.0%). The post-protocol group had a significantly higher proportion of patients with dyslipidemia (38.6% vs 23.2%, p=0.038) and a lower proportion of unfit patients (33.7% vs 55.6%, p=0.005) compared to the pre-protocol group. No significant differences were observed in other baseline characteristics between the two groups (Table 1).

Primary outcome

The implementation of the multidisciplinary protocol was associated with a significant reduction in 30-day mortality, decreasing from 16.2% in the pre-protocol group to 6.0% in the post-protocol group (p=0.037) (Fig 2). Kaplan-Meier analysis demonstrated improved 30-day overall survival in the post-protocol group (94.0% vs 83.8%, log-rank test p=0.034) (Fig 3).

Secondary outcomes

Multivariable Cox regression analysis revealed that protocol implementation was associated with a 49.1% reduction in the hazard of 30-day mortality (adjusted HR 0.509, 95% CI 0.175-1.478, p=0.213), although this did not reach statistical significance. Cardiac arrest (aHR 8.180, 95% CI 3.382-19.785, p<0.001) and unfit patient status (aHR 6.420, 95% CI 1.876-21.965, p=0.003) emerged as independent predictors of 30-day mortality (Table 2).

No significant differences were observed between the pre- and post-protocol groups in terms of estimated blood loss, blood replacement, use of aortic balloon occlusion, length of procedure, ICU stay, or hospital stay (Table 3).

The post-protocol group demonstrated significant reductions in postoperative complications, notably myocardial ischemia (7.2% vs 21.2%, p=0.015) and

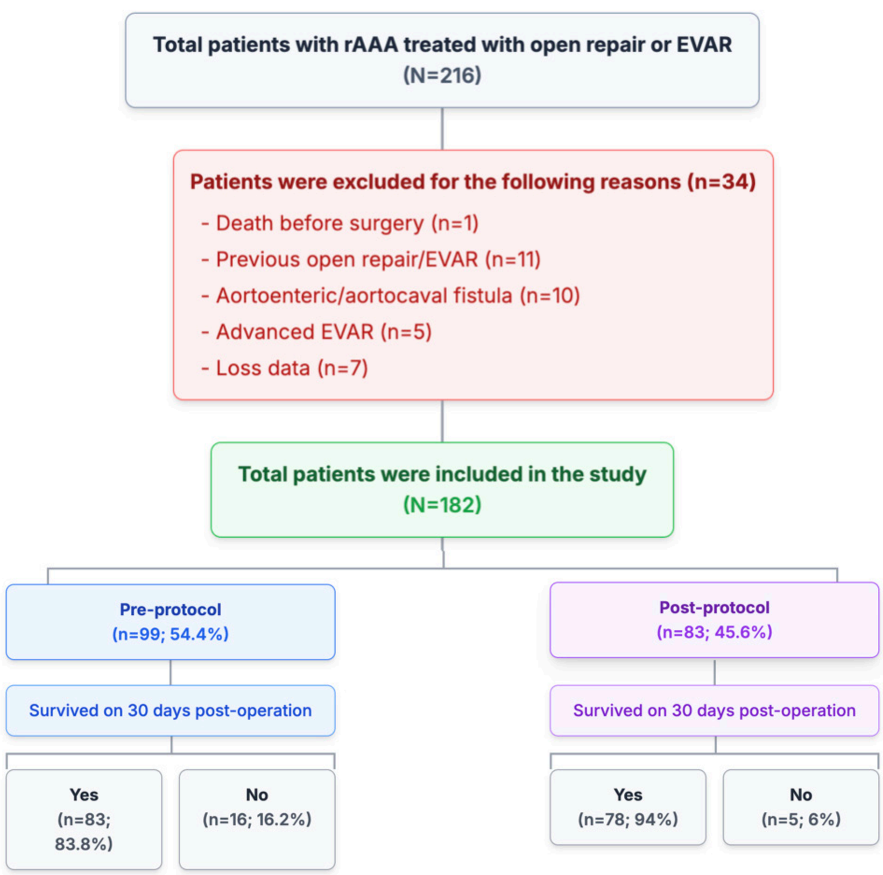

Fig 2. Patient flow and survival rates for AAA treatment with open repair or EVAR.

TABLE 1. Demographic and clinical characteristics of patients before and after implementation of the multidisciplinary protocol.

Characteristic	Total (n=182)	Pre-Protocol (n=99)	Post-Protocol (n=83)	P-value
Demographics				
Age (years); mean ± SD	72.3 ± 10.7	71.5 ± 11.3	73.3 ± 10.0	0.280
Age > 80 years; n (%)	38 (20.9%)	16 (16.2%)	22 (26.5%)	0.127
Male sex; n (%)	153 (84.1%)	85 (85.9%)	68 (81.9%)	0.604
Comorbidities				
Hypertension; n (%)	136 (74.7%)	73 (73.7%)	63 (75.9%)	0.870
Dyslipidemia; n (%)	55 (30.2%)	23 (23.2%)	32 (38.6%)	**0.038**
Type 2 Diabetes mellitus; n (%)	35 (19.2%)	16 (16.2%)	19 (22.9%)	0.338
Coronary artery disease; n (%)	30 (16.5%)	16 (16.2%)	14 (16.9%)	1.000
Cerebrovascular disease; n (%)	16 (8.8%)	7 (7.1%)	9 (10.8%)	0.527
Renal insufficiency; n (%)	40 (22.0%)	22 (22.2%)	18 (21.7%)	1.000
COPD; n (%)	16 (8.8%)	11 (11.1%)	5 (6.0%)	0.345
Current smoking; n (%)	26 (14.3%)	16 (16.2%)	10 (12.0%)	0.564
Clinical Presentation				
Unfit patient status; n (%)	83 (45.6%)	55 (55.6%)	28 (33.7%)	**0.005**
Hemodynamic instability; n (%)	76 (41.8%)	44 (44.4%)	32 (38.6%)	0.515
Cardiac arrest; n (%)	16 (8.8%)	11 (11.1%)	5 (6.0%)	0.345
Transferred from other hospitals; n (%)	146 (80.2%)	79 (79.8%)	67 (80.7%)	1.000
Laboratory Parameters				
Hemoglobin (g/dl); mean ± SD	9.6 (2.2%)	9.8 (2.1%)	9.5 (2.2%)	0.363
Hematocrit (%); mean ± SD	29.4 (6.4%)	29.7 (6.4%)	29.0 (6.6%)	0.456
Creatinine (mg/dl); median (min, max)	1.5 (0.1, 9.6)	1.6 (0.1, 9.0)	1.5 (0.5, 9.6)	0.426

Statistically significant P-values are in bold
Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation

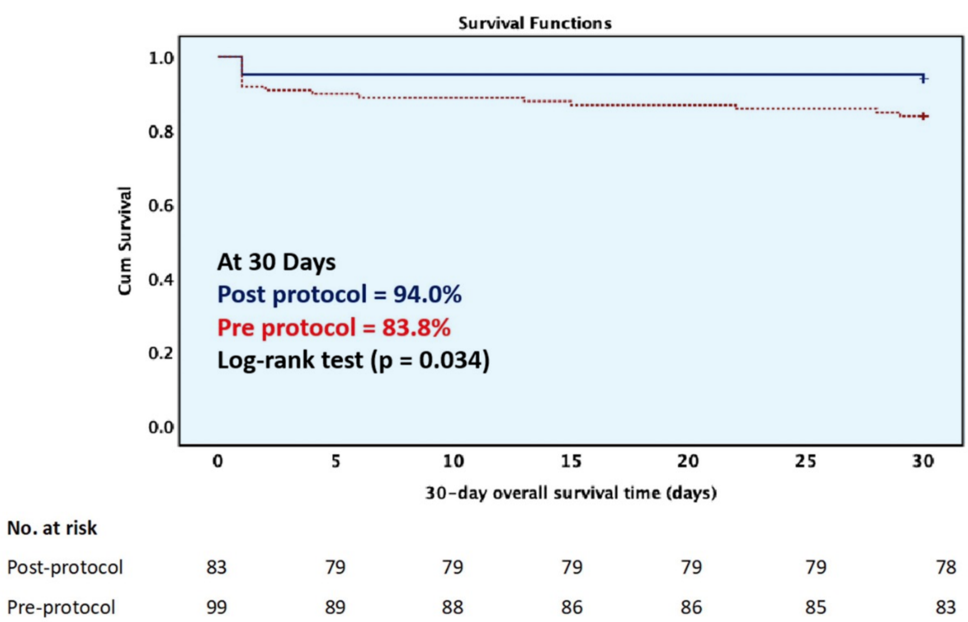

Fig 3. Kaplan-Meier curves illustrating 30-day overall survival in patients with rAAA.

TABLE 2. Univariable and multivariable Cox proportional hazards analyses of factors associated with 30-day overall survival.

Factor	Univariable Model		Multivariable Model	
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Protocol Implementation		**0.046**		0.461
Post-protocol	1.000 (Reference)		1.000 (Reference)	
Pre-protocol	2.778 (1.018, 7.585)		1.491 (0.515, 4.314)	
Clinical Factors				
Dyslipidemia	0.712 (0.261, 1.944)	0.508	0.580 (0.211, 1.594)	0.291
Unfit patient status	7.701 (2.267, 26.159)	**0.001**	6.420 (1.876, 21.965)	**0.003**
Hemodynamic instability	4.829 (1.768, 13.192)	0.002	2.503 (0.794, 7.891)	0.117
Cardiac arrest	10.125 (4.222, 24.282)	**<0.001**	8.180 (3.382, 19.785)	**<0.001**

Abbreviations: HR, hazard ratio; CI, confidence interval
Values <1.0 indicate factors associated with improved survival; values >1.0 indicate factors associated with increased mortality risk
Statistically significant P-values are in bold

TABLE 3. Intraoperative and postoperative characteristics before and after implementation of the multidisciplinary protocol.

Variable	Total (n=182)	Pre-Protocol (n=99)	Post-Protocol (n=83)	P-value
Intraoperative Parameters				
Estimated blood loss (ml); median (min, max)	700 (20, 22500)	500 (20, 21000)	1000 (20, 22500)	0.300
Estimated blood loss > 2000 ml; n (%)	59 (32.4%)	30 (30.3%)	29 (34.9%)	0.612
Blood replacement (Units); median (min, max)	4 (0, 40)	4 (0, 19)	4 (0, 40)	0.521
Aortic balloon occlusion; n (%)	70 (38.5%)	39 (39.4%)	31 (37.3%)	0.897
Procedure duration (minutes); median (min, max)	180 (35, 530)	180 (55, 530)	180 (35, 435)	0.425
Postoperative Course				
ICU length of stay (days); median (min, max)	4.5 (0, 90)	4 (0, 90)	5 (0, 64)	0.412
Hospital length of stay (days); median (min, max)	15 (1, 221)	16 (1, 189)	15 (1, 221)	0.865

Abbreviation: ICU, intensive care unit

septicemia (1.2% vs 20.2%, p<0.001), compared to the pre-protocol group. No significant differences were observed in other complications (Tables 4 and 5).

Subgroup analysis

When stratified by repair technique, both EVAR and OSR demonstrated trends toward reduced 30-day mortality during the post-protocol period. EVAR mortality decreased from 18.1% to 6.8%, whereas OSR mortality fell from 11.1% to 5.1%. Regarding complications, no significant difference was observed between EVAR and OSR during either the pre- or post-protocol period.

TABLE 4. Postoperative complications before and after implementation of the multidisciplinary protocol.

Complication	Total (n=182)	Pre-Protocol (n=99)	Post-Protocol (n=83)	P-value
Organ-Related Complications				
Myocardial ischemia; n (%)	27 (14.8%)	21 (21.2%)	6 (7.2%)	**0.015**
Congestive heart failure; n (%)	14 (7.7%)	6 (6.1%)	8 (9.6%)	0.533
Respiratory failure; n (%)	22 (12.1%)	9 (9.1%)	13 (15.7%)	0.260
Renal failure requiring hemodialysis; n (%)	31 (17.0%)	19 (19.2%)	12 (14.5%)	0.517
Ischemic colitis; n (%)	17 (9.3%)	9 (9.1%)	8 (9.6%)	1.000
Abdominal compartment syndrome; n (%)	41 (22.5%)	21 (21.2%)	20 (24.1%)	0.775
Wound dehiscence; n (%)	4 (2.2%)	2 (2.0%)	2 (2.4%)	1.000
Infectious Complications				
Chest infection; n (%)	42 (23.1%)	28 (28.3%)	14 (16.9%)	0.100
Wound infection; n (%)	8 (4.4%)	7 (7.1%)	1 (1.2%)	0.119
Intraabdominal infection; n (%)	6 (3.3%)	4 (4.0%)	2 (2.4%)	0.690
Graft infection; n (%)	2 (1.1%)	2 (2.0%)	0 (0%)	0.501
Septicemia; n (%)	21 (11.5%)	20 (20.2%)	1 (1.2%)	**<0.001**
Urinary tract infection; n (%)	6 (3.3%)	2 (2.0%)	4 (4.8%)	0.414
Other				
Perioperative reintervention; n (%)	45 (24.7%)	20 (20.2%)	25 (30.1%)	0.170

Statistically significant P-values are in bold

TABLE 5. Comparison of complications between EVAR and OSR in pre- and post-protocol periods.

Complication	Pre-Protocol				Post-Protocol			
	Total	EVAR	OSR	P-value	Total	EVAR	OSR	P-value
Cardiac/Pulmonary								
Myocardial ischemia; n (%)	21 (21.2%)	17 (23.6%)	4 (14.8%)	0.498	6 (7.2%)	5 (11.4%)	1 (2.6%)	0.207
Congestive heart failure; n (%)	6 (6.1%)	4 (5.6%)	2 (7.4%)	0.663	8 (9.6%)	5 (11.4%)	3 (7.7%)	0.717
Respiratory failure; n (%)	9 (9.1%)	5 (6.9%)	4 (14.8%)	0.251	13 (15.7%)	7 (15.9%)	6 (15.4%)	1.000
Renal/Gastrointestinal								
Renal failure requiring hemodialysis; n (%)	19 (19.2%)	11 (15.3%)	8 (29.6%)	0.184	12 (14.5%)	5 (11.4%)	7 (17.9%)	0.590
Ischemic colitis; n (%)	9 (9.1%)	7 (9.7%)	2 (7.4%)	1.000	8 (9.6%)	6 (13.6%)	2 (5.1%)	0.272
Abdominal compartment syndrome; n (%)	21 (21.2%)	14 (19.4%)	7 (25.9%)	0.670	20 (24.1%)	11 (25.0%)	9 (23.1%)	1.000
Infectious								
Chest infection; n (%)	28 (28.3%)	20 (27.8%)	8 (29.6%)	1.000	14 (16.9%)	7 (15.9%)	7 (17.9%)	1.000
Wound infection; n (%)	7 (7.1%)	5 (6.9%)	2 (7.4%)	1.000	1 (1.2%)	1 (2.3%)	0	1.000
Intraabdominal infection; n (%)	4 (4.0%)	3 (4.2%)	1 (3.7%)	1.000	2 (2.4%)	2 (4.5%)	0	0.496
Graft infection; n (%)	2 (2.0%)	2 (2.8%)	0	1.000	0	0	0	-
Septicemia; n (%)	20 (20.2%)	15 (20.8%)	5 (18.5%)	1.000	1 (1.2%)	1 (2.3%)	0	1.000
Urinary tract infection; n (%)	2 (2.0%)	2 (2.8%)	0	1.000	4 (4.8%)	3 (6.8%)	1 (2.6%)	0.619
Other								
Wound dehiscence; n (%)	2 (2.0%)	1 (1.4%)	1 (3.7%)	0.473	2 (2.4%)	2 (4.5%)	0	0.496
Perioperative reintervention; n (%)	20 (20.2%)	15 (20.8%)	5 (18.5%)	1.000	25 (30.1%)	16 (36.4%)	9 (23.1%)	0.28

Abbreviations: EVAR, endovascular aneurysm repair; OSR, open surgical repair

DISCUSSION

This 13-year retrospective cohort study demonstrates that implementation of a comprehensive multidisciplinary protocol for managing rAAA is associated with significantly improved 30-day survival rates and reduced postoperative complications. Our findings underscore the potential of structured, team-based approaches to enhance outcomes in time-critical vascular emergencies. However, in multivariable analysis, protocol implementation was associated with only a non-significant reduction in mortality.

The potential for such significant mortality reduction challenges the traditionally high mortality rates associated with rAAA, which have been reported to range from 50% to 80% in various studies.[11,12] The observed reduction in 30-day mortality from 16.2% to 6.0% after protocol implementation is remarkable and exceeds improvements reported in previous studies. For instance, Takei et al. observed a decrease in mortality from 22.5% to 9.6% after introducing an endovascular-first protocol.[13] In contrast, the IMPROVE trial reported a 30-day mortality rate of 35.4% for endovascular strategy and 37.4% for open repair.[14] Our more substantial improvement may be attributed to the comprehensive nature of our protocol, which encompassed not only treatment selection but also streamlined processes, enhanced communication, and standardized postoperative care.

The protocol's significant reductions in major postoperative complications, particularly myocardial ischemia and septicemia, indicate benefits beyond immediate survival. This comprehensive improvement in outcomes can be attributed to several factors: rapid mobilization of a multidisciplinary team, standardized decision-making processes, preparedness for both EVAR and OSR, proactive measures like massive transfusion protocols and aortic balloon occlusion preparation, and streamlined postoperative care. These elements, which align with recent guidelines and expert consensus statements on rAAA management,[15,16] collectively contribute to swift, coordinated care, optimized treatment selection, reduced delays, improved hemodynamic stability, reduced end-organ damage, and earlier recognition and management of complications.

The reduction in myocardial ischemia is consistent with studies showing that protocolized care can improve cardiac outcomes in high-risk surgical patients.[17] However, our improvement exceeds that reported in many studies, warranting further investigation into the specific elements of our protocol that may have contributed to this outcome.

The trend towards increased use of endovascular aortic repair (EVAR) in our study mirrors global patterns in rAAA management.[8] EVAR is frequently employed as the initial treatment strategy for rAAA in many institutions, given its reported benefits in patient outcomes. However, unlike some studies that attribute improved outcomes solely to the adoption of EVAR,[3] our results suggest that a comprehensive protocol can enhance outcomes across both EVAR and open surgical repair (OSR). Furthermore, the post-protocol group exhibited a notable increase in the proportion of open surgical repair (OSR) for rAAA patients (pre-protocol: 27% vs post-protocol: 47%). This shift is likely attributable to the protocolized use of advanced preoperative imaging, which facilitates enhanced patient selection for the most appropriate operative approach. So, patient with anatomy suitable for EVAR underwent EVAR, whereas those without suitable for EVAR underwent open surgical repair

Our multivariable analysis identified cardiac arrest (aHR 8.180, 95% CI 3.382-19.785) and unfit patient status (aHR 6.420, 95% CI 1.876-21.965) as independent predictors of 30-day mortality. These findings are consistent with previous studies[18,19] and highlight the critical importance of rapid assessment and intervention in rAAA cases, as well as the need for careful patient selection and optimization when possible. The strong association between cardiac arrest and mortality underscores the time-sensitive nature of rAAA management and supports the emphasis our protocol places on rapid activation of the multidisciplinary team and streamlined transfer processes. The impact of patient fitness on outcomes highlights the potential benefit of prehabilitation programs for high-risk patients with known AAAs, although the emergency nature of rAAA often precludes such interventions.

While our study provides compelling evidence for the benefits of a multidisciplinary protocol in rAAA management, we acknowledge several limitations. First, as a single-center study, our results may not be fully generalizable to all healthcare settings. Second, the observational nature of the study precludes definitive causal inferences about the protocol's impact. Third, evolving technology, increased operation expertise and general improvements in critical care over the study period may have contributed to the observed outcomes.

Future research should focus on validating these findings in multicenter, randomized controlled trials. Additionally, investigating the long-term outcomes and cost-effectiveness of protocol-driven rAAA management would provide valuable insights for healthcare policy and resource allocation. Exploring the potential of artificial intelligence and machine learning in refining risk stratification and decision-making processes for rAAA could also be a fruitful avenue for future studies.[20]

CONCLUSION

In conclusion, our study supports that a comprehensive multidisciplinary protocol for rAAA management can reduce postoperative complications and improve short-term survival, despite multivariable analysis showing a non-significant reduction in mortality. These findings have important implications for vascular surgery practice and highlight the potential of systems-based approaches to enhance outcomes in acute care settings. As the landscape of rAAA management continues to evolve, embracing standardized, team-based protocols may be key to further reducing mortality and morbidity in this challenging patient population.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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DECLARATIONS

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Conflict of Interest

All authors declare that they have no personal or professional conflicts of interest, and received no financial support from the companies that produce and distribute the drugs, devices, or materials described in this report.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, K.C., N.P., and N.T.; Investigation, N.T., C.R., C.W., K.H., N.S., S.H., T.P., K.P.; Formal analysis, S.T., N.T., K.C.; Visualization and writing – N.P., N.T., K.C. original draft, N.T., K.C; Writing – review and editing, N.P., N.T., K.C.; Supervision, K.C. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None.

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