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Cost-Effectiveness of Open Repair of Abdominal Aortic Aneurysms with a Novel Perioperative Protocol

Dissertation

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1. Original-Artikel: **„Cost-Effectiveness of Open Repair of Abdominal Aortic Aneurysms with a Novel Perioperative Protocol"**

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Clinical Research

Cost-Effectiveness of Open Repair of Abdominal Aortic Aneurysms with a Novel Perioperative Protocol

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Background: In 2015, a novel perioperative protocol (nPOP), comprising of 19 evidence-based interventions, was adopted as a standard practice for open repair of abdominal aortic aneurysms (AAA) at the Humanitas Clinical and Research Center (Milan, Italy). Its implementation translated into lower complication rates, faster ambulation and return of bowel function, better nausea/vomiting and pain control, and, consequently, a shorter length of hospital stay. Because value of a patient's care cycle can be defined as clinical outcomes relative to costs, we aimed to analyze the cost-effectiveness of nPOP compared to the previously implemented protocols.

Methods: Three groups were identified and retrospectively analyzed: (A) 66 patients (September 2007 to March 2009) treated according to the traditional protocol; (B) 225 patients (April 2009 to March 2015) treated in line with a transitional protocol, incorporating 5 perioperative interventions; and (C) 103 patients (April 2015 to February 2019) treated according to nPOP. For each group a monetary value of required clinical resources and the actual total cost per patient from admission to discharge were determined. The following were analyzed (including nurse and anesthesiologist time): diagnostic tests, medications, materials, operating time, surgical team time, blood transfusion, ward stay, and intensive care unit stay. Two indicators of effectiveness were determined based on the postoperative outcomes: complication-free incidents and relative shortening of hospitalization time. A cost (€) of an improvement in effectiveness (%) was calculated.

Results: Alongside enhancement of clinical outcomes, nPOP constituted the cheapest approach. It consumed the least human and material resources, resulting in the direct reduction in the overall clinical cost per patient. The length-of-stay variable provided the largest reduction in total costs. The actual total clinical cost per patient in Group C was 26% lower than in Group A (4,437€ vs. 6,005€) and 39% lower than in Group B (4,437€ vs. 7,305€). Every unit of enhancement of clinical outcomes was 2.43 times more expensive for the traditional protocol and 2.23 times more costly for the transitional protocol compared to nPOP, making it the most cost-effective.

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Conclusions: The nPOP for AAA open repair is not inferior to other perioperative protocols while allowing for efficient utilization of limited hospital resources, thus creating a high social value. The proposed methods for cost-effectiveness analysis are easily reproducible and therefore can be applied in future projects ranging from a micro- to a macro-economic scale.

INTRODUCTION

The social value of a patient's care cycle can be defined as clinical outcomes relative to their costs.[1] The efficient utilization of limited hospital resources has always been crucial for the economic sustainability of the healthcare system. The importance of this mindful resource management becomes paramount during times of global health disasters, such as the ongoing COVID-19 pandemic, where the already stretched and often under-funded budget must be shifted toward waves of new infections, while the rest of the health system cannot afford to collapse.

In the past few years, the perioperative protocol for elective open surgical repair (OSR) of abdominal aortic aneurysms (AAA) was modified twice in Humanitas Clinical and Research Center (Milan, Italy). The traditional protocol was followed by a transitional period, accounting for a learning curve of the multidisciplinary team. In 2015, the novel perioperative protocol (nPOP), based on principles of enhanced recovery and fast-track programs (ER/FT), was successfully implemented. This led to a significant improvement in clinical outcomes on many levels, and among others, translated into lower rates of complications, as well as shorter hospitalization times.

Having demonstrated the noninferiority of clinical outcomes associated with nPOP compared to other implemented protocols,[2] the aim of the current study is to analyze its financial sustainability by means of cost-effectiveness analysis (CEA). CEA is an economic tool that seeks to either improve the beneficial effect within predetermined cost restraints or to minimize costs of reaching a prespecified objective (Fig. 1).[3] It is commonly used in the public health sector, where the desired outcomes cannot be simply measured in monetary units, but nevertheless, the cost minimization of achieving these goals is of the essence.

MATERIALS AND METHODS

Patient Selection

Three groups (A, B, C) were identified and retrospectively analyzed based on the applied perioperative protocol for the elective AAA open repair at the Humanitas Clinical and Research Center (Milan, Italy).[2] These perioperative patient management modifications stemmed from periodic revisions of internal protocols, aiming to enhance the quality of patient care within the constraints of hospital resources.

Group A: 66 patients (September 2007 to March 2009) treated according to the traditional approach
Group B: 225 patients (April 2009 to March 2015) treated in line with a transitional protocol, which incorporated 5 perioperative ER/FT interventions
Group C: 103 patients (April 2015 to February 2019) treated according to nPOP, including 19 perioperative ER/FT items

Table I depicts the differences between the 3 perioperative protocols.

In total, 394 consecutive patients, who underwent elective OSR of infrarenal and juxtarenal aortic aneurysms (with or without involvement of iliac arteries), were analyzed. The exclusion criteria were as follows: ruptured or symptomatic AAA, interventions with concomitant repair of any other organ, as well as previous aortic repair. Due to a different etiology, hemodynamic impact, and perisurgical risks, the patients undergoing aortic surgery for occlusive disease were also excluded from the analysis. During the study period, 134 patients were treated via endovascular aortic repair (EVAR); these patients were not included in the study. Provided that the arterial anatomy was suitable for EVAR, indications to endovascular approach were the following: patient's preference, severe chronic obstructive pulmonary disease, cardiac failure, ''frozen'' abdomen, and/or associated comorbidities (i.e., impaired neurological or social conditions) that would hamper adherence to the protocol.

The patients were similar in terms of demographic characteristics and presented comorbidities, with one exception where those in Group C were on average slightly older. The aneurysm morphologies and types of reconstruction were comparable across the 3 groups (Table II).

All the patients signed an informed consent permitting scientific management of their data.

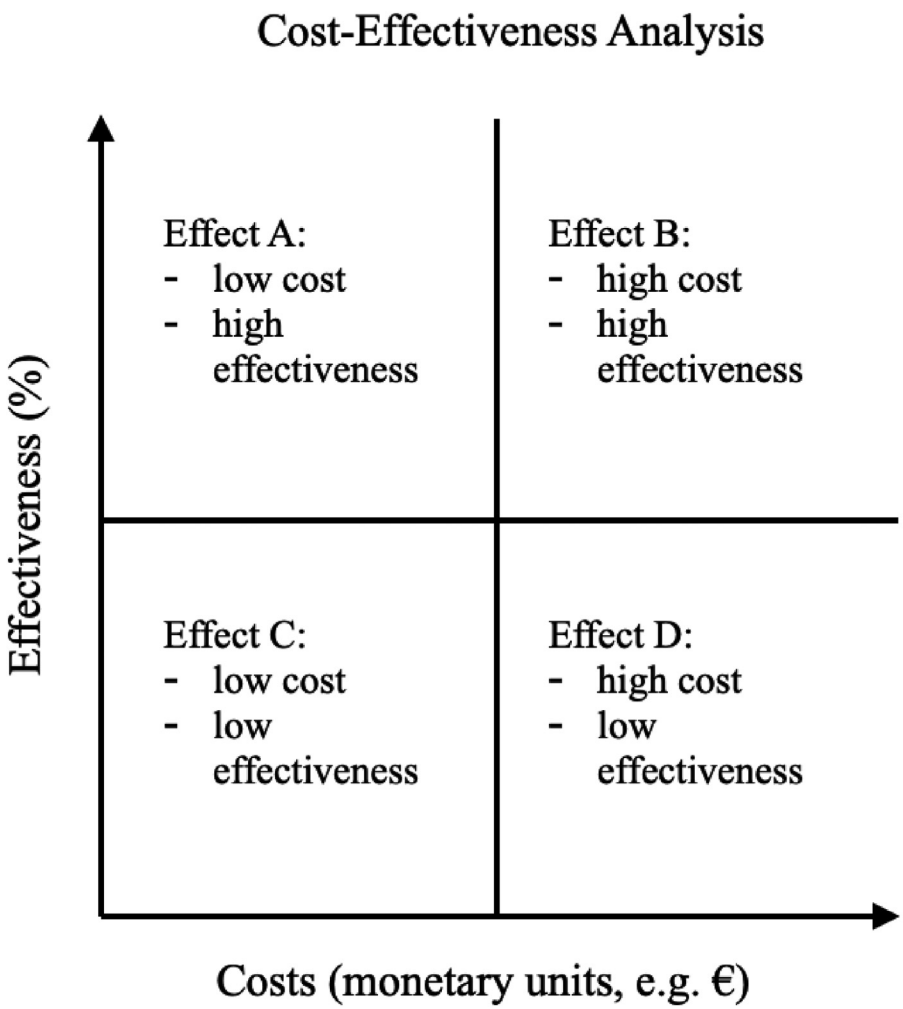

Fig. 1. The graph represents the essence of relationship between costs and effectiveness, depicting 4 different effects, where A is the most cost-effective and D the least cost-effective.

The initial study was approved by the local ethics committee (retrospective study 23/19). No further institutional review board approval was required for this cost-effectiveness extension of the initial study.

Cost-Effectiveness Analysis Definition

CEA is the ratio between the cost and effectiveness of a given intervention. Effectiveness is the ability of producing a predetermined outcome. Therefore, CEA allows for a calculation of the cost required to gain a unit of benefit, and can be portrayed as follows:

$$Cost/_{Benefit} = Cost\ per\ unit\ of\ benefit$$

In the healthcare setting, the generalized unit of benefit is equivalent to a unit of improvement in a health outcome. In this study, a unit of improvement in a health outcome was termed ''a unit of improvement in intervention's effectiveness.''

Indicators of effectiveness.. Two clinical postoperative outcomes were chosen to measure the effectiveness of the perioperative protocols: total complication rates (Clavien-Dindo complication groups II–V)[4] and postsurgical hospitalization time. In order to establish the benefit variable which could then be applied to the CEA formula, these values had to be converted into their corresponding positive counterparts (stimulants): total complication-free incidents and shortening of relative postsurgical hospitalization time, respectively. In the study, they were termed as ''indicators of treatment effectiveness'' (Table III).

Because Group A represented the traditional perioperative approach it was treated as a reference

Table I. Comparison of the implementation of perioperative ER/FT elements between the 3 cohorts[2]

Perioperative ER/FT elements		Traditional perioperative protocol (Group A, 66 patients)	Transitional perioperative protocol (Group B, 225 patients)	Novel perioperative protocol (Group C, 103 patients)
Preoperative				
#1	Counseling			x
#2	No fasting			x
#3	Carbohydrate loading			x
Intraoperative				
#4	No central venous catheter			x
#5	Active normothermia			x
#6	Goal-directed fluids			x
#7	Pre-emptive analgesia			x
#8	No evisceration			x
#9	No drainages		x	x
Postoperative				
#10	Opioid-sparing analgesia		x	x
#11	PONV prophylaxis			x
#12	Restrictive ICU			x
#13	Early nasogastric tube removal		x	x
#14	Early urinary catheter removal			x
#15	No prokinetic drugs			x
#16	Early enteral feeding		x	x
#17	No intravenous hydration			x
#18	Early mobilization		x	x
#19	Early discharge			x
Total ER/FT elements applied		0	5	19

PONV, post-operative nausea and vomitting.

baseline for creating a relative comparison assessment between all the groups, meaning that in the case of Group A the reduction in the hospitalization time equated to 0%.

The Clavien-Dindo classification has been applied to measure surgical morbidity.[4] Complication groups II—V of the Clavien-Dindo classification were included in the analysis. Group II complications were categorized as minor and groups III and IV as major. Group V complications—mortality—occurred only in the transitional cohort. The observation period was carried out for 30 postsurgical days.

Total clinical cost.. For each group the monetary value of required clinical resources and the actual total clinical cost (€) per patient from admission to discharge were determined. The following parameters were analyzed (including nurse and anesthesiologist time): diagnostic tests, medications, materials, operating time, surgical team time (1 hr for admission and discharge, 1 hr per day of ward stay, and operation time with 3 surgeons present), blood transfusion, ward stay, and intensive care unit (ICU) stay. Throughout the study period, the required preoperative examinations were mostly completed in advance in an outpatient clinic. These diagnostic tests, if not performed externally, were included in the analysis. The resource use was converted to direct costs using 2021 € values.

Statistical Analysis

Regarding the protocol data, nominal variables were presented as a number (%), ordinal variables were described as a median with an interquartile range, and variables considered to be continuous were expressed as a mean with a standard deviation. To establish uniform ''indicators of treatment effectiveness,'' ordinal values were also converted into a number (%). The cost data were taken directly from the hospital accounting system and represent the actual cost per patient. The group comparison was performed using a chi-squared test for categorical variables, a Mann-Whitney *U*-test for ordinal variables, and a one-way analysis of variance and a two-tailed paired *t*-test for continuous variables. Statistical significance was set at a *P* value of 0.05 or less.

Cost-Effectiveness Analysis Calculation

CEA of a given protocol was presented as the ratio between the actual total clinical cost per patient from admission to discharge (€) and the average value of factors indicating treatment effectiveness.

Table II. Patients' demographic features and surgical characteristics

Patient and surgical data	Traditional perioperative protocol (Group A, 66 patients)	Transitional perioperative protocol (Group B, 225 patients)	Novel perioperative protocol (Group C, 103 patients)	*P*-value
Age (years)	70 ± 8	71 ± 7	73 ± 8	0.007 A
Sex, male	64 (97)	210 (93)	92 (89)	0.156 C
Hypertension	50 (76)	170 (76)	82 (80)	0.710 C
Diabetes mellitus	9 (14)	37 (16)	17 (17)	0.849 C
COPD	15 (23)	42 (19)	25 (24)	0.467 C
Dyslipidemia	21 (32)	113 (50)	50 (49)	0.028 C
CKD	7 (11)	20 (9)	13 (13)	0.578 C
ASA score 3–4	36 (55)	139 (62)	60 (58)	0.531 C
Infrarenal aneurysm	47 (71)	164 (73)	81 (79)	0.260 C
Juxtarenal aneurysm	0	14 (6)	5 (5)	0.116 C
Inclusion of iliac arteries	19 (29)	47 (21)	17 (17)	0.160 C
Aorto-aortic reconstruction	45 (68)	136 (60)	74 (72)	0.109 C

Data are presented as mean ± standard deviation or number (%).[2]
A, one-way analysis of variance test; ASA, American Society of Anesthesiologists; C, chi-squared test with Fisher correction; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

After adaptation to the ex-post CEA for the evaluation of clinical treatments we assumed the following:

$$CEA_{ex\ post} = \frac{\sum_{k=1}^{m} ATCC_c (1+r)^t}{\frac{1}{n}\sum_{j=1}^{n} ITE_j}$$

where $ATCC_c$ is the actual total clinical cost for c cohort (Group A, B, or C), k is the number of ATCC components (1…m), t represents the number of capitalization years for a given cohort, r is the interest rate for period t, and ITE_j is a j-indicator of treatment effectiveness, with n representing the number of indicators.

Rehabilitation Costs

For completion, the analysis was expanded by the postdischarge rehabilitation costs that occurred in Group C, where 52% of patients completed their recovery in a rehabilitation center. Importantly, these patients did not require medical attention. Instead, they were assisted in regaining full physical strength, as well as further implementation of healthy lifestyle habits. A transfer to a rehabilitation center was voluntary. Of note, none of the patients from Groups A and B were directed to the postdischarge rehabilitation due to the unavailability of such facilities at that time.

RESULTS

Financial Outcomes

The financial outcomes are represented in Table IV. The nPOP consumed the least human and material resources, constituting the cheapest approach. The postsurgical length-of-stay variable provided the largest reduction in total costs. The reduction in the postoperative hospitalization time and the complication rates in the nPOP group, led to savings in diagnostic examinations and human resources.

The nPOP, alongside enhancement of clinical outcomes, permitted optimization of the use of hospital resources on 2 economic levels:

1. Micro-level (institutional) it allowed for a direct reduction in the overall clinical resources cost; for the nPOP group it was 26% lower than the traditional approach (4,437€ vs. 6,005€) and 39% lower than the transitional protocol (4,437€ vs. 7,305€).
2. Macro-level (systemic) it decreased the social opportunity costs which, in turn, generated a potential to increase the hospital capacity for accommodation of more patients in need, thus constituting an additional social value.

We reported a significant cost reduction in preadmission diagnostic tests in Group C. This stemmed from a shift toward performing these tests externally and was unrelated to the implementation of the new operative protocol.

Despite having implemented 5 perioperative items, the total clinical cost per patient in Group B appeared the highest of all. Upon closer analysis we observed the following:

1. Within Group B the use of a bifurcated prosthesis was the most common (40% compared to 32% in Group A and 28% in Group C;

Table III. Postoperative outcomes as measure of effectiveness of the implemented care plans with their corresponding indicators of treatment effectiveness

Postoperative outcomes/ indicators of effectiveness	Traditional perioperative protocol (Group A, 66 patients)	Transitional perioperative protocol (Group B, 225 patients)	Novel perioperative protocol (Group C, 103 patients)	*P*-value
Complications, *n* (%)	14 (21)	25 (11)	8 (8)	0.019 C
Minor	2 (3)	10 (4)	3 (3)	0.747 C
Arrythmia	1	9	1	
Pneumonia	1	1	2	
Major	12 (18)	13 (6)	5 (5)	0.001 C
NSTEMI	0	0	1	
ARDS	0	3	0	
AKI	2	1	0	
Ureteral lesion	0	1	0	
Hemoperitoneum	0	1	2	
Bowel perforation	0	1	0	
Ileus	3	1	0	
Urinary incontinence	0	0	1	
Wound infection	2	1	0	
Incisional hernia	2	0	0	
Limb ischemia	2	2	0	
Lymphorrhea	1	2	1	
Complication-free incidents, %	79	89	92	
Postoperative hospitalization time (days), median (IQR)	6 (5–7)	5 (4–7)	3 (2–4)	A–B < 0.001 D B–C < 0.001 D A–C < 0.001 D
Shortening of relative median postoperative hospitalization time, %	0	17	50	

Data presented as median (interquartile range), or number (%).[2]
AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; C, chi-squared test; D, Mann-Whitney *U*-test; IQR, interquartile range; NSTEMI, non-ST elevation myocardial infarction.

$P = 0.109$), which raised the costs of materials and medications. The nature of the complications that occurred in Group B might have also influenced these costs.

2. More blood products were transfused in Group B (560 ± 220 vs. 490 ± 242 in Group A and 420 ± 178 in Group C; $P = 0.152$).[2]
3. A significant increase in the ICU admissions was observed in Group B (27% compared to 15% in Group A and 17% in Group C; $P = 0.044$),[2] which generated a considerable cost variation.

Cost-Effectiveness Analysis Results

A gain in effectiveness of each protocol was represented by an average of 2 clinical outcomes, expressed as their incremental effects in % (indicators of treatment effectiveness). For each group, these were, in turn, divided by the actual total clinical cost per patient. After substituting to the ex-post CEA formula, the results depicted in Table V were obtained.

As shown, in comparison to nPOP, every unit of improvement in intervention's effectiveness was 2.43 times more expensive in the case of the traditional protocol and 2.23 times more expensive in the case of the transitional protocol. This made nPOP by far the most cost-effective from all applied perioperative care plans.

Having expanded the results for Group C by the postdischarge rehabilitation costs, the actual total clinical cost increased by 48.21%, placing nPOP in the middle on a financial scale (Table VI). Importantly, even with the inclusion of rehabilitation costs, nPOP remained the most cost-effective.

DISCUSSION

Protocols' Development

Elective OSR of AAA, constituting a more definitive treatment solution compared to the endovascular repair, remains a first-choice approach for fit patients with life expectancy of more than 10 years.[5] Its

Table IV. Comparison of clinical costs for treatment of AAA via open repair according to 3 different perioperative protocols

Actual clinical costs (€)	Traditional perioperative protocol (Group A, 66 patients)	Transitional perioperative protocol (Group B, 225 patients)	Novel perioperative protocol (Group C, 103 patients)
Diagnostic tests	1,085	1,043	432
Preadmission	355	227	192
Inpatient	730	817	240
Materials and medications	580	836	602
Operating room time	1,421	1,586	1,370
Surgical team time	1,073	1,164	863
Blood products	68	158	70
Stay	1,778	2,518	1,101
Ward	1,369	1,438	751
ICU[a]	409	1,080	350
Total clinical cost	6,005	7,306	4,437

Data represent actual costs per patient taken from the hospital accounting system. Algorithm for the cost calculation of surgical team time: 1 hr for admission and discharge, 1 hr per day of ward stay, operation time with 3 surgeons present. Costs of operation and ICU stay included nurse and anesthesiologist time. Cost of ward stay included nurse working time.
[a]Of note, ICU was indicated only for high-risk patients thanks to the in-ward telemetry monitoring.

significant perioperative burden,[6] however, overshadows the long-term efficacy of this treatment modality and therefore had to be addressed.

The 3 cohorts were identified based on the differences in perioperative patient management strategies applied at a given time. Group A represents the traditional perioperative approach, acting as a reference group. Group B illustrates a period when first 5 ER/FT elements were introduced to test their feasibility as well as compliance. This period was associated with a significant learning curve of surgeons, nurses, and anesthesiologists due to a strong multidisciplinary aspect of the implemented changes. Finally, Group C demonstrates an advanced stage of the ER/FT application in daily clinical practice, being based on an ensemble of 19 intertwined perioperative elements. These evidence-based interventions were adopted from existing ER/FT programs widely implemented in other surgical specialties, whereas their application in vascular surgery remains very limited.[7–11] Because one of the pillars of the ER/FT programs is cost reduction,[12] there was a need to assess the financial sustainability of the nPOP. For this, CEA was used as it is not merely limited to the monetary data. Instead, it allows for the interpretation of dynamics between outcomes and costs, where the improvement in both these factors constitutes the goal of the public health sector.

Rationale for the Indicators of Effectiveness

A financial analysis of the 3 protocols was broadened by the effectiveness aspect. CEA is an economic tool used to evaluate costs and outcomes of a new intervention compared to an existing one,[13,14] with the aim of reducing costs while achieving the prespecified objective or improving outcomes, keeping the expenses unchanged. The results are presented as additional cost per additional unit of benefit gained.[15] In order to carry out such an analysis, it is fundamental to identify suitable measures of effectiveness (indicators of effectiveness). These depend on the objective of the intervention under assessment.[16]

The aim of the modifications of perioperative patient management strategies is to enhance recovery through reduction in both postoperative complications and length of hospitalization. To reflect this exact objective, the positive counterparts of the 2 abovementioned outcomes were chosen as the indicators of treatment effectiveness.

The mission of the institution revolves around a balance between a patient-centralized multidisciplinary treatment pathway and organizational efficiency. Humanitas Clinical and Research Center acts as a case study of the Harvard Business School for its organizational model, which combines economic and social responsibility.[17] Both, complication rates and hospitalization time carry a strong socioeconomic component, having a profound impact on patients as individuals and the healthcare system on an institutional level.

Finally, reduction in complication rates, shortening of the hospitalization time, and cutting costs form a triad of main objectives of the ER/FT programs.[12,18] Presenting and analyzing their mutual

Table V. Cost effectiveness of the perioperative protocols across the 3 cohorts

Components of the cost-effectiveness analysis	Traditional perioperative protocol (Group A, 66 patients)	Transitional perioperative protocol (Group B, 225 patients)	Novel perioperative protocol (Group C, 103 patients)
Actual total clinical cost (€ per patient)	6.005	7.306	4.437
ITE, %			
Complication-free incidents ratio	79	89	92
Shortening of relative postoperative hospitalization time	0	17	50
Average total ITE	39.5	53	71
Cost effectiveness of the protocols (€ per % point of effectiveness)	152.03	137.85	62.49

ITE, indicator of treatment effectiveness.

interdependence with full and partial application of the ER/FT principles might add a new dimension to understanding the concept of ER. In the study, both indicators of treatment effectiveness were granted with an equal weight. A collective CEA for their average was conducted since the 2 outcomes form equally important pillars of ER/FT programs.

Enhanced Recovery and Fast-Track in Vascular Surgery

Due to a limited implementation of ER/FT programs for vascular interventions, the available studies on the topic within the specialty also remain scarce. Nevertheless, the ER/FT programs proved to be both clinically efficacious and cost effective for major thoracoabdominal operations across a variety of surgical fields in the short term.[19–21] The available literature highlights the role of the length-of-stay parameter as the main contributor to cost reduction, which coincides with our results.

Opportunity Cost

Importantly, cost reduction comes in 3 different types: cost savings, avoided costs, and opportunity costs. Opportunity cost saving is probably less obvious than other types of cost reduction, but nevertheless, it has a crucial role for the efficient functioning of the healthcare system.

The concept of opportunity cost expresses the fundamental relationship between scarcity and choice, meaning that with limited resources all demands cannot be met. Opportunity cost is the evaluation of the most highly regarded of the rejected alternatives or opportunities. In other words, it is the value that is given up or sacrificed.[22]

With respect to the objectives of this study, opportunity cost occurs if a less efficient protocol uses more hospital resources than its next best alternative. These additional hospital resources, if spared, could be used in a productive way, which, when economically valued adds an ''extra cost'' to the less efficient protocol.

Precise calculation of the opportunity cost is complex when expressed by the downstream benefits of the technology under evaluation and hence it is beyond the scope of this analysis. In this study, the downstream benefits constituted of shorter duration of hospital stay and fewer postoperative complications. Shorter hospitalization allowed for admission and treatment of more patients, which apart from being profitable for the hospital, provided a strong social benefit. Moreover, an added economic value was generated through a faster return to work. This could be valued via a multiplication of extra workdays and average daily wage in the economy.[23,24] Lower complication rates allowed for savings in performed diagnostic tests as well as the provided therapy and treatment.

Discharge Criteria and Rehabilitation

The main discharge criteria for all the groups included the following: optimal pain control, appropriate bowel function, and adequate care support at home. A postdischarge transfer to a rehabilitation center is a relatively new opportunity offered by the Italian healthcare system, which is why it was available exclusively for the patients in Group C. It is impossible to predict how many patients from Groups A and B would have been transferred to a rehabilitation center if such an option had been granted at that time and, importantly, how (if at all) it would have influenced their length of hospital stay. We speculate that the hospitalization time would have remained relatively unchanged in Group C without the possibility of a transfer to a rehabilitation center as the goal of these institutions is to assist in restoring the patients' physical capacity once the medical stage of recovery is completed. The

Table VI. Postdischarge rehabilitation costs for Group C

Number of patients directed to rehabilitation, *n* (%)	54 (52%)
Average number of days spent in a rehabilitation clinic per patient	16
Daily cost per patient, €	255
Actual total clinical cost expanded by the average rehabilitation costs, €	6.576
Cost effectiveness of the nPOP including postdischarge rehabilitation (€ per % point of effectiveness)	92.62

lack of adequate support at home might have been a factor that prolonged the hospital stay of some patients in Groups A and B.

Limitations

The issue of a nonuniform implementation of rehabilitation opportunities across the cohorts can be seen as a study limitation. Because it was applied only to Group C, its position in the CEA is unclear and hence this analysis was presented separately. Importantly, even with the inclusion of the rehabilitation costs, nPOP remained the most cost-effective.

Another limitation might be represented by a short observation period. Because there were no readmissions in Group C, a longer follow-up would probably not provide any significant contribution to the assessment of costs and early outcomes of the adopted protocols.

Standardization of the perioperative protocols and reinforcement of their implementation with a dedicated multidisciplinary team were strongly emphasized in all cases. Specifically, all the listed preoperative and intraoperative items have been incorporated into our daily standard practice, meaning they were applied to all the patients. The variation in the implementation of the postoperative items depended on the operative course and immediate complications; for example, if ICU monitoring was required, adherence to the protocol had to be adjusted. All efforts were undertaken to minimize any protocol deviations, while ensuring best patient care at the same time.

With the advancement of endovascular technologies, the frailest patients were directed to undergo EVAR (34% of patients across the full study period), which makes the results prone to a certain degree of a selection bias. All the interventions were performed in a high-volume center (>30 AAA cases/year)[25] with at least 1 surgical consultant present; however, the implementation of nPOP coincides with a change in the head of the department. Finally, improvements that tend to occur over time in every medical field and surgical team cannot be disregarded when analyzing groups of patients placed consecutively in time.

Next Steps

Development of Guidelines for Enhanced Recovery after vascular interventions could aid promotion and implementation of the perioperative changes. Considering the overwhelming global burden of cardiovascular diseases, acceleration of the recovery process could not only improve the hospital bed turnover rate but also boost the efficiency of the healthcare system.

Authors' mission is to continue advocating novel approaches in vascular surgery, making it less invasive and more cost-effective. The ongoing project revolves around implementation of ER/FT principles for abdominal surgeries in the Department of Vascular Medicine in the Heart and Vascular Center Hamburg-Eppendorf (Germany).

This analysis could provide a template for assessment of input-outcome interactions from an institutional to a systemic level. It could allow for a better understanding of the complexity of the public health sector and aid in decision-making, which in the end translates into better healthcare and smarter resource management.

CONCLUSIONS

The nPOP for AAA open repair is not inferior to other implemented protocols, while allowing for efficient and cost-effective utilization of limited hospital resources, thus creating a high social value. Given the significant global burden of cardiovascular diseases, this CEA could provide a template for healthcare optimization from a micro- to a macroeconomic scale. Multicenter studies should be encouraged to further affirm the conclusions. Development of Enhanced Recovery Guidelines targeting vascular interventions could promote and assist in the implementation of the protocol across centers.

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2. Darstellung der Publikation

2.1. Introduction

Despite the continuously expanding application of enhanced recovery after surgery (ERAS)-like pathways in many surgical arenas, their implementation in the field of vascular surgery remains limited. An increasing pool of evidence, supporting the superiority of ERAS-like pathways over the traditional peri-operative patient management strategies, has been well documented in the literature.[1-3]

The primary objective of these protocols is a reduction of peri-operative stress, conventionally associated with major surgeries. The protocol implementation has proven to accelerate the recovery process, and thus, decrease the complication rates and shorten the length of hospital stay.[4]

The ERAS-like pathways derive from a broad collection of pre-, intra-, and post-operative evidence-based elements. There is a strong focus on multimodality of patient care, meaning that a spectrum of peri-operative interventions is applied to achieve a synergic positive effect on the recovery process. Often one goal, for example pain control, can be achieved through diverse interventions, applied at different levels, and acting via various mechanisms. Another highlight of the ERAS-like protocols is the multidisiplinarity of treatment, consisting of close collaboration between surgeons, anaesthetists, nurses, and physiotherapists.[4]

With the rapid development of new endovascular technologies, little attention has been paid to optimisation of the open vascular repair. Especially in the case of the abdominal aortic aneurysms (AAA), the booming stent-graft development greatly overshadows the potential advantages carried by the open repair. The open surgical repair (OSR) of AAA is, however, still considered a more definitive treatment solution and has been recommended by the European Society for Vascular Surgery as the first-choice strategy for fit patients with a life expectancy of more than 10 to 15 years.[5] It is favoured for patients with connective tissues diseases and provides a good alternative for those with unsuitable anatomy for an endovascular treatment. Moreover, OSR remains an important bail-out solution when complications occur. The burden related to operative stress, anaesthesia, time to restoration of functional capacity and length of hospital stay, unfortunately remain overwhelming in the case of OSR for AAA and should be addressed.

2.2. Materials and Methods

2.2.1. Impact of the full ERAS-like protocol on selected post-operative outcomes

Patient Selection and Study Design

From September 2007 to February 2019, at the Vascular Surgery department of Humanitas Clinical and Research Centre (Milan, Italy), 394 consecutive patients undergoing elective OSR of infrarenal and juxtarenal aortic aneurysms, with or without involvement of iliac arteries, were

retrospectively analysed. The emergency cases along with patients treated via an endovascular aortic repair (EVAR) were excluded from the analysis. Other exclusion criteria were: ruptured or symptomatic AAA, concomitant repair of other organ, aortic re-intervention, and aortic surgery for occlusive disease.[6]

During the study period, the peri-operative protocol was modified twice. These changes stemmed from systematic revisions of standard operating procedures, aiming to optimise quality of care and hospital resources.

Three consecutive patient cohorts were identified based on the applied peri-operative care plan (Table 1):

- Group A: 66 patients (September 2007 to March 2009) treated according to the traditional approach;
- Group B: 225 patients (April 2009 to March 2015) treated in line with a transitional protocol, which incorporated 5 peri-operative ERAS interventions;
- Group C: 103 patients (April 2015 to February 2019) treated according to a complete ERAS-like protocol, which included 19 peri-operative elements.

Table 1. Comparison of the implementation of peri-operative ERAS-like elements between the 3 cohorts.[6]

PERI-OPERATIVE ERAS ELEMENTS			TRADITINAL PERI-OP PROTOCOL (Group A, 66 patients)	TRANSITIONAL PERI-OP PROTOCOL (Group B, 225 patients)	ERAS-like PERI-OP PROTOCOL (Group C, 103 patients)
PRE-OP	#1	counselling			x
	#2	avoidance of fasting			x
	#3	carbohydrate loading			x
INTRA-OP	#4	avoid central venous catheter			x
	#5	active normothermia			x
	#6	goal-directed fluid			x
	#7	pre-emptive analgesia			x
	#8	avoid evisceration			x
	#9	avoid drainage		x	x
POST-OP	#10	opioid sparing analgesia		x	x
	#11	PONV prophylaxis			x
	#12	restrictive ICU			x
	#13	early nasogastric tube removal		x	x
	#14	early urinary catheter removal			x
	#15	avoid prokinetic drugs			x
	#16	early enteral feeding		x	x
	#17	avoid IV hydration			x
	#18	early mobilization		x	x
	#19	early discharge			x
TOTAL ERAS ELEMENTS APPLIED			**0**	**5**	**19**

ERAS- enhanced recovery after surgery, PONV- post-operative nausea and vomiting, ICU- intensive care unit, IV- intravenous

All the patients signed an informed consent allowing for management of their data for scientific purposes. The study was approved by the local Ethics Committee (retrospective study 23/19).

Aims of the Study

The primary end point of the initial study was to assess the impact of the full ERAS-like protocol on early post-operative complication rates. Length of hospital stay represented one of the secondary end points pertinent to the current study.

Grade II and above complications according to the Clavien-Dindo classification,[7] that occurred within 30 post-operative days were recorded. Group II was considered minor, groups III and IV-major. Group I complications were not included in the analysis. Pain was considered significant if reported above a score of 4 according to the numeric rating scale.

Statistical Analysis

Nominal variables were presented as a number (%). Ordinal variables were described as a median with an interquartile range. Continuous variables were expressed as a mean with a standard deviation. The group comparison was performed using a chi-squared test for categorical variables, a Mann-Whitney U test for ordinal variables, a one-way analysis of variance and a two-tailed paired t test for continuous variables. Statistical significance was set at a P value of 0.05 or less.[6]

2.2.2. Financial and Cost-Effectiveness Analysis

Financial Data

The actual total clinical cost (€) per patient from admission to discharge was determined for each cohort. The following were analysed, including nurse and anaesthesiologist time: diagnostic tests, medications, materials, operating time, surgical team time (1 hr for admission and discharge, 1 hr per day of ward stay, and operation time with 3 surgeons present), blood transfusion, ward stay, and intensive care unit (ICU) stay. The required pre-operative examinations, if not performed externally, were included in the analysis. The resource use was converted to direct costs using 2021 € values.[8]

Cost-Effectiveness Analysis Calculation

Cost-Effectiveness Analysis (CEA) is the ratio between the cost and effectiveness of a given intervention. Effectiveness represents the ability of reaching a predetermined positive outcome (benefit). Thus, CEA is used to calculate the cost required to gain a unit of benefit.

In the healthcare setting, the unit of benefit equates to a unit of improvement in a health outcome. In this study, the health outcome was understood as the efficacy of a given peri-operative protocol and, in turn, was represented by the “indicators of effectiveness”.

Two clinical post-operative outcomes were chosen to measure the protocols’ efficacy: total complication rates (Clavien-Dindo groups II-V) and length of hospital stay. These values were converted into the corresponding stimulants: total complication-free incidents and relative shortening of the hospitalisation time, respectively. In turn, they were termed ‘‘indicators of treatment effectiveness’’.

Since Group A represented the traditional peri-operative protocol it acted as a reference baseline for creating a relative comparison assessment between all the cohorts. Therefore, the reduction in the hospitalisation time for Group A equated to 0%.

Accordingly, CEA of a given peri-operative protocol was represented by the ratio between the actual total clinical cost per patient from admission to discharge (€) and the average value of ''indicators of treatment effectiveness''.

After adaptation to the ex-post CEA for the evaluation of clinical treatments we assumed the following:

$$CEA_{ex\ post} = \frac{\sum_{k=1}^{m} ATCC_c(1+r)^t}{\frac{1}{n}\sum_{j=1}^{n} ITE_j}$$

where $ATCC_c$ is the actual total clinical cost for c cohort (Group A, B, or C), k is the number of ATCC components (1... m), t represents the number of capitalisation years for a given cohort, r is the interest rate for period t, and ITE_j is a j-indicator of treatment effectiveness, with n representing the number of indicators.[8]

Rehabilitation Costs

The analysis was expanded by the post-discharge rehabilitation costs that occurred exclusively in Group C, where 52% of patients completed their recovery in a rehabilitation centre.[6,8] Importantly, no medical attention was required at that point and a transfer to a rehabilitation centre was voluntary. None of the patients from Groups A and B were directed to a rehabilitation centre due to the unavailability of such facilities at that time.

2.3. Results

2.3.1. Peri-operative Protocol Evaluation

Demographic characteristics and presented comorbidities were similar among all the patients, with one exception where those in Group C were on average slightly older. The aneurysm morphologies and types of reconstruction were comparable (Table 2).

Table 2. Patients' demographic features and surgical characteristics.[6]				
PATIENT AND SURGICAL DATA	TRADITINAL PERI-OP PROTOCOL (Group A, 66 patients)	TRANSITIONAL PERI-OP PROTOCOL (Group B, 225 patients)	ERAS-like PERI-OP PROTOCOL (Group C,103 patients)	p-value
Age, *years*	70 ± 8	71 ± 7	73 ± 8	0.007 A
Sex, *male*	64 (97)	210 (93)	92 (89)	0.156 C
Hypertension	50 (76)	170 (76)	82 (80)	0.710 C
Diabetes mellitus	9 (14)	37 (16)	17 (17)	0.849 C
COPD	15 (23)	42 (19)	25 (24)	0.467 C
Dyslipidaemia	21 (32)	113 (50)	50 (49)	0.028 C
CKD	7 (11)	20 (9)	13 (13)	0.578 C
ASA Score 3-4	36 (55)	139 (62)	60 (58)	0.531 C
Infrarenal aneurysm	47 (71)	164 (73)	81 (79)	0.260 C
Juxtarenal aneurysm	0	14 (6)	5 (5)	0.116 C
Incl. of iliac arteries	19 (29)	47 (21)	17 (17)	0.160 C
Aorto-aortic reconstruction	45 (68)	136 (60)	74 (72)	0.109 C
Data presented as mean ± SD or number (%) A= one-way Anova test, B= t-test for two independent means, C= Chi-squared test with Fisher correction COPD- chronic obstructive pulmonary disease, CKD- chronic kidney disease, ASA- American Society of Anaesthesiologists				

There was an overall improvement in the recorded 30-day post-operative outcomes for Group C (Table 3). The mortality rates were comparable; there were two deaths in Group B and zero deaths in Groups A and C (P = 0.470). There was a downward trend for complication rates over time (21% vs 10% vs 8%; P = 0.019). Although minor complications remained unchanged (P = 0.747), the major ones significantly dropped in Groups B (6%) and C (5%) in comparison to Group A (18%; P = 0.001). No difference in cardiopulmonary complications was observed (3% vs 6% vs 4%; P = 0.575). The median day of discharge differed drastically between the groups (P < 0.001), with the median discharge on day 6 for Group A, day 5 for Group B, and day 3 for Group C.[6]

Table 3. Post-operative outcomes as measure of effectiveness of the implemented care plans with their corresponding indicators of treatment effectiveness.[8]

POST-OP OUTCOMES/ INDICATORS OF EFFECTIVENESS	TRADITINAL PERI-OP PROTOCOL (Group A, 66 patients)	TRANSITIONAL PERI-OP PROTOCOL (Group B, 225 patients)	ERAS-like PERI-OP PROTOCOL (Group C,103 patients)	p-value
Complications, n (%)	14 (21)	25 (11)	8 (8)	0.019 C
Minor	2 (3)	10 (4)	3 (3)	0.747 C
o Arrythmia	1	9	1	
o Pneumonia	1	1	2	
Major	12 (18)	13 (6)	5 (5)	0.001 C
o NSTEMI	0	0	1	
o ARDS	0	3	0	
o AKI	2	1	0	
o Ureteral lesion	0	1	0	
o Hemoperitoneum	0	1	2	
o Bowel perforation	0	1	0	
o Ileus	3	1	0	
o Urinary incontinence	0	0	1	
o Wound infection	2	1	0	
o Incisional hernia	2	0	0	
o Limb ischemia	2	2	0	
o Lymphorrhea	1	2	1	
Mortality, n (%)	0	2 (1)	0	0.470 C
Complication-free incidents, n (%)	52 (79)	198 (88)	95 (92)	
Post-operative hospitalisation time in days, median (IQR)	6 (5-7)	5 (4-7)	3 (2-4)	A-B <0.001 D B-C <0.001 D A-C <0.001 D
Shortening of relative median post-operative hospitalisation time, %	0	17	50	

AKI- acute kidney injury, ARDS- acute respiratory distress syndrome, NSTEMI- non-ST elevation myocardial infarction
Data presented as median (interquartile range), or number (%)
C= Chi-squared test, D= Mann-Whitney U test

Throughout the study period, the patients were admitted on the day before surgery and all the required examinations were performed in advance. Length of stay or hospitalisation time is a post-operative day +1.[6]

From these results the indicators of effectiveness were derived – complication-free incidents and shortening of relative median post-operative hospitalisation time, respectively (Table 3).

2.3.2. Financial Outcomes

The full ERAS-like protocol consumed the least human and material resources constituting the cheapest approach. The post-operative length-of-stay variable provided the largest reduction in total costs. The reduction in the post-operative hospitalisation time and the complication rates in group C led to savings in diagnostic examinations and human resources (Table 4).[8]

Table 4. Comparison of average clinical costs of treating AAA via open repair according to three different peri-operative protocols.[8]

AVERAGE CLINICAL COSTS IN €	TRADITINAL PERI-OP PROTOCOL (Group A, 66 patients)	TRANSITIONAL PERI-OP PROTOCOL (Group B, 225 patients)	ERAS-like PERI-OP PROTOCOL (Group C, 103 patients)
DIAGNOSTIC TESTS • PRE-ADMISSION • INPATIENT	1085 355 730	1043 227 817	432 192 240
MATERIALS & MEDICATIONS	580	836	602
OPERATING ROOM TIME	1421	1586	1370
SURGICAL TEAM TIME	1073	1164	863
BLOOD PRODUCTS	68	158	70
STAY • WARD • ICU	1778 1369 409	2518 1438 1080	1101 751 350
TOTAL AVG. CLINICAL COST	**6005**	**7306**	**4437**

Algorithm for the cost calculation of surgical team time: 1 hr for admission and discharge, 1 hr per day of ward stay, operation time with 3 surgeons present;
Costs of operation and ICU stay included nurse and anaesthesiologist time;
Cost of ward stay included nurse working time
* Of note, ICU was indicated only for high-risk patients thanks to the in-ward telemetry monitoring.

Thanks to the implementation of the full ERAS-like protocol, the use of hospital resources could be optimized on 2 economic levels:

1. Micro-level (institutional) – the ERAS-like protocol allowed for a direct reduction in the overall clinical resources cost; these were 26% lower in group C than for the traditional approach (4,437€ vs. 6,005€) and 39% lower than for the transitional protocol (4,437€ vs. 7,305€).

2. Macro-level (systemic) – the ERAS-like protocol decreased the opportunity costs which, in turn, generated a potential to increase the hospital capacity for more patients in need, thus, constituting an additional social value.[8]

The pre-operative diagnostic tests were mainly performed externally for Group C. The associated cost reduction was, therefore, unrelated to the implementation of the new operative protocol.

Despite having implemented 5 perioperative items, the total clinical cost per patient in Group B appeared the highest of all. Upon closer analysis we observed the following:

1. Within Group B the use of a bifurcated prosthesis was the most common (40% compared to 32% in Group A and 28% in Group C; P= 0.109), which raised the material costs.
2. More blood products were transfused in Group B, which together with the nature of the occurred complications might have resulted in higher spendings.
3. An increase in the ICU admissions in Group B (27% compared to 15% in Group A and 17% in Group C; P= 0.044) most definitely generated considerable cost variations.[8]

2.3.3. Cost-Effectiveness Analysis Results

In comparison to the full ERAS-like protocol, every unit of improvement in intervention's effectiveness was 2.43 times more expensive in the case of the traditional protocol and 2.23 times more expensive in the case of the transitional protocol. This made the full ERAS-like protocol the most cost-effective (Table 5).[8]

Table 5. Cost effectiveness of the peri-operative protocols across the three cohorts.[8]

Components of the Cost-Effectiveness Analysis		TRADITINAL PERI-OP PROTOCOL (Group A, 66 patients)	TRANSITIONAL PERI-OP PROTOCOL (Group B, 225 patients)	ERAS-like PERI-OP PROTOCOL (Group C, 103 patients)
Average total clinical costs (€ per patient)		6.005	7.306	4.437
Indicator of treatment effectiveness (ITE, %)	Complication-free incidents ratio	79	88	92
	Shortening of relative postoperative hospitalization time	0	17	50
Average total ITE		39,5	52,5	71
Cost effectiveness of the treatment protocols, (€ per % point of effectiveness)		152,03	139,16	62,49

ITE- indicator of treatment effectiveness

Table 6. Post-discharge rehabilitation costs for Group C.[8]	
Number of patients directed to rehabilitation, n (%)	54 (52%)
Avg. number of days spent in a rehabilitation clinic	16
Avg. daily cost, €	255
Avg. total clinical cost expanded by the avg. rehabilitation costs, €	6.576
Cost effectiveness of the ERAS-like protocol including post-discharge rehabilitation, € per % point of effectiveness	92,62

Having expanded the results for Group C by the post-discharge rehabilitation costs, the actual total clinical cost increased by 48.21%, placing it in the middle on a financial scale. Importantly, even with the inclusion of rehabilitation costs, Group C remained the most cost-effective (Table 6).

2.4. Discussion

With the ongoing focus on the expansion of the minimally invasive treatment methods, the modernisation of the traditional surgery has lately not received much attention. The significant peri-operative burden of OSR for AAA continues to overshadow its long-term efficacy. Our goal was to optimise the elective open aortic repair, making it more appealing to the patients during the decision-making process when planning the aneurysm treatment.

In the initial phase of the study, 3 cohorts were identified based on the adopted peri-operative protocol. Group A represented the traditional peri-operative approach, acting as a reference group. Group B illustrated a period when first 5 ERAS elements were introduced, creating a buffer for a learning curve of all the members of the ERAS-like multidisciplinary team. Finally, Group C featured an advanced stage of the complete ERAS-like application. This last protocol was based on an ensemble of 19 peri-operative elements, aiming to expedite recovery. Having compared the 3 cohorts, we noted a significant improvement in the complication rates and hospitalisation time, thus demonstrating the non-inferiority of ERAS-like pathways compared to the traditional ones.[6,8]

Due to the limited implementation of the ERAS-like protocols for vascular interventions, the available studies within the specialty remain scarce and rather of questionable quality. The number of applied peri-operative elements varies greatly, and compliance is rarely analysed.[9,10] Nevertheless, there is a wide spectrum of data, stemming from other surgical fields, that support the clinical efficacy and cost effectiveness of ERAS for major thoracoabdominal operations. The available literature highlights the role of the length-of-stay parameter as the main contributor to cost reduction, which coincides with our results.[1,11,12]

The social value of a patient's care cycle can be defined as clinical outcomes relative to their costs.[13] The smart use of limited hospital resources has always been of the essence for the economic sustainability of the healthcare on the systemic level. The efficient resource management

becomes even more so important during times of global health disasters, such as the recent COVID-19 pandemic, where the already narrow budget had to be suddenly shifted towards the management of new infection waves. At the same time, naturally, the rest of the healthcare system could not afford to collapse, and the high-quality care had to be continuously provided for all those in need.

One of the pillars of the ERAS-like programs is cost reduction, therefore, our further objective was to assess the financial sustainability of the implemented ERAS-like protocol.[14,15] This was achieved with CEA, which is not merely limited to the monetary data but, instead, it allows for the interpretation of dynamics between outcomes and costs, where the improvement of both these factors constitutes the goal of the public health sector. CEA is an economic tool used to evaluate costs and outcomes of a new intervention compared to an existing one. Its aim is to reduce costs while achieving the prespecified objective, or to improve outcomes, keeping the expenses unchanged.[16,17] The results are presented as a ratio of additional cost per additional unit of benefit gained.[18] To carry out such an analysis, it is fundamental to identify suitable measures of effectiveness, the so called "indicators of effectiveness". These, in turn, depend on the objective of the intervention under assessment.[8,19]

For this analysis, the treatment effectiveness was measured by two outcomes – complication rates and hospitalisation time. These two specific outcomes are strongly associated with enhanced recovery and reflect the most important goals of the protocol modifications. Together with cost reduction they represent a triad of key ERAS objectives.[14]

To fully embrace the benefits of the mindful and efficient resource management, it is paramount to understand that cost reduction comes in 3 different types: cost savings, avoided costs, and opportunity costs. Opportunity cost saving is by far less obvious than other types of cost reduction, but nevertheless, it plays a fundamental role in the functioning of a well-designed healthcare system. It can be portrayed as the evaluation of the most highly regarded of the rejected alternatives or opportunities, making up the value that is given up or sacrificed.[20] With respect to the objectives of this study, opportunity cost occurs if a less efficient protocol uses more hospital resources than its next best alternative. These additional hospital resources, if spared, could be used in a productive way, which, when economically valued adds an ''extra cost'' to the less efficient protocol.

The issue of a nonuniform implementation of rehabilitation opportunities across the cohorts can be seen as a study limitation. Since it was applied only to Group C, its position in the CEA is unclear. Thus, this analysis was presented separately. Importantly, even with the inclusion of the rehabilitation costs, the full ERAS-like protocol remained the most cost-effective.

Another limitation might be represented by a short observation period. Due to the lack of readmissions in Group C, however, a longer follow-up would probably not lead to any significant alterations in the cost-effectiveness analysis. It would also most probably not carry any direct relevance for the evaluation of the peri-operative protocols.

Standardization of the peri-operative protocols and their thorough implementation via a highly trained multidisciplinary team were strongly emphasized in all cases. Specifically, all the listed pre-operative and intra-operative items have been incorporated into our standard operating procedures, meaning they were applied to all the patients. The variation in the implementation of the post-operative items depended on the operative course and immediate complications; for example, if ICU monitoring was required, adherence to the protocol had to be adjusted. All efforts were undertaken to minimize any protocol deviations, while ensuring best patient care at the same time. All the interventions were performed in a high-volume centre (>30 AAA cases/ year)[21] with at least 1 surgical consultant present, nevertheless, improvements that tend to occur over time in every medical field and surgical team cannot be disregarded when analysing groups of patients placed consecutively in time.[8]

The recent development of Guidelines for Enhanced Recovery after vascular interventions will aid propagation and implementation of the peri-operative changes.[22] Having a dedicated definite list of recommendations will most likely improve the quality and uniformity of the data on ERAS for vascular operations. Considering the overwhelming global burden of cardiovascular diseases, acceleration of the recovery process could not only improve the hospital bed turnover rate but also boost the efficiency of healthcare on an institutional and systemic level.

Authors' mission is to continue advocating novel approaches in vascular surgery, making it less invasive and more cost-effective. The ongoing project revolves around implementation of the ERAS-like principles for open aortic surgeries in the Department of Vascular Medicine in the Heart and Vascular Centre Hamburg-Eppendorf (Germany).

This analysis could provide a template for assessment of input-outcome interactions from an institutional to a systemic level. It could allow for a better understanding of the complexity of the public health sector and aid in decision-making, which in the end translates into better healthcare and smarter resource management.

2.5. Conclusions

The ERAS-like protocol for AAA open repair is not inferior to other implemented protocols, while allowing for efficient and cost-effective utilization of limited hospital resources, thus creating a high social value. Given the significant global burden of cardiovascular diseases, this study could provide tools and template for healthcare optimization from a micro- to a macro- economic scale. Multicentre studies should be encouraged to further affirm the conclusions.

2.6. Abbreviations

ERAS – Enhanced Recovery After Surgery
AAA – abdominal aortic aneurysm
OSR – open surgical repair
EVAR – endovascular aortic repair
POD – post-operative day
PONV – post-operative nausea and vomiting
ICU – intensive care unit
IV – intravenous
COPD – chronic obstructive pulmonary disease
CKD – chronic kidney disease
ASA – American Society of Anaesthesiologists
AKI – acute kidney injury
ARDS – acute respiratory distress syndrome
NSTEMI – non-ST elevation myocardial infarction
ITE – indicator of treatment effectiveness

2.7. References

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3. Zusammenfassung

The burden of operative stress and time to restoration of functional capacity remains significant in the case of open surgical repair of abdominal aortic aneurysms (AAA), overshadowing its long-term benefits with respect to endovascular repair.
Despite the recent expansion of the enhanced recovery or fast track protocols (ER/FT), their application in the field of vascular surgery remains limited. These novel care plans consist of multimodal evidence-based interventions, implemented pre-, intra- and post-operatively, in order to shorten hospitalization time, decrease complications and cut costs.

In 2021 we published a single-center retrospective analysis, comparing the traditional, transitional and novel (nPOP) peri-operative protocols for AAA open repair. Upon the nPOP implementation, a significant improvement was noted in the complication rates and hospitalization time. Since value of a patient's care cycle can be defined as clinical outcomes relative to costs, a year later we expanded the study, performing a comparative financial and cost-effectiveness analysis for the three cohorts, which constitutes this dissertation. The nPOP resulted in the direct reduction in the overall clinical cost per patient and was by far the most cost-effective. The nPOP for AAA open repair is not inferior to other peri-operative protocols. Furthermore, it allows for efficient utilization of limited hospital resources, thus creating a high social value.

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Die Belastung durch den operativen Stress und die Zeit bis zur Wiederherstellung der Funktionsfähigkeit ist bei der offenen chirurgischen Reparatur von Bauchaortenaneurysmen (BAA) signifikant und überschattet deren langfristige Vorteile gegenüber der endovaskulären Therapie.
Trotz der aktuellen zunehmenden Verbreitung von "Enhanced Recovery"- oder "Fast Track"-Protokollen (ER/FT) ist ihre Anwendung im Bereich der Gefäßchirurgie weiterhin limitiert. Diese neuartigen Versorgungsverfahren bestehen aus multimodalen, evidenzbasierten Interventionen, die prä-, intra- und post-operativ implementiert werden, um die Krankenhausverweildauer zu verkürzen, Komplikationen zu reduzieren und Kosten zu senken.

Im Jahr 2021 veröffentlichten wir eine retrospektive Single-Center Analyse, in der die traditionellen, die Übergangs- und die neuartigen (nPOP) perioperativen Protokolle für die offene BAA-Reparatur verglichen wurden. Bei der Einführung des nPOP wurde eine signifikante Verbesserung der Komplikationsraten und der Krankenhausaufenthaltsdauer festgestellt. Da der Wert des Versorgungszyklus eines Patienten als klinische Ergebnisse im Verhältnis zu den Kosten definiert werden kann, haben wir ein Jahr später die Studie erweitert und eine vergleichende Finanz- und Kosten-Wirksamkeits-Analyse für die drei Kohorten durchgeführt, die Gegenstand dieser Dissertation ist. Das nPOP führte zu einer direkten Senkung der klinischen Gesamtkosten pro Patient und war bei weitem am kosteneffektivsten. Das nPOP für die offene BAA-Reparatur ist anderen perioperativen Protokollen nicht unterlegen. Außerdem ermöglicht es eine effiziente Verwendung der begrenzten Krankenhausressourcen und ist somit von hohem sozialem Wert.

4. Erklärung des Eigenanteils an der Publikation

Die Arbeit wurde als Kooperationsprojekt zwischen der Klinik für Gefäßmedizin, Universitäres Herz- und Gefäßzentrum Hamburg des Universitätsklinikums Hamburg Eppendorf, und des Humanitas Clinical and Research Center in Mailand, Italien, durchgeführt. Die Publikation der Arbeit erfolgte in Annals of Vascular Surgery.

Untenstehende Tabelle gibt eine Übersicht der Arbeitsteilung bei der Erstellung der Publikation.

	Karolina Daria Malik	Efrem Civilini	Krzysztof Kazimierz Malik	Elena Vanni	Tilo Kölbel	Eike Sebastian Debus
Konzeption und Studiendesign	X	X	X			X
Datenerhebung und -analyse	X		X	X		
Verfassen der Publikation	X		X	X		
Kritische Anpassungen und Lektorat	X	X	X		X	X

5. Danksagungen

I would like to thank my Mentor and Supervisor of this research project – Prof. Sebastian Debus for his tremendous kindness and unparalleled enthusiasm towards all the projects we undertake, including this dissertation. Thank you for all the opportunities you have granted me with, your guidance and support.

This publication mirrors the rewarding time spent at the Humanitas Clinical and Research Center in Milan and so I thank my Italian Mentor and Friend Prof. Efrem Civilini for shaping me into someone I have always wanted to be.

At last, I dedicate this work to my Dad – my beloved supporter, motivator, role model and collaborator. Thank you for your economical inspirations, undivided attention, and deepest engagement in everything we undertake.

6. Lebenslauf

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CAREER

01/09/2010 – 26/04/2013	**General Education Public High School No. II with Bilingual Division in Opole, Poland**
28/06/2013	**Matriculation Examination, Opole, Poland**
01/10/2013 – 11/07/2019	**Medicine, International Medical School, University of Milan (Italy)** • Graduation thesis: „Enhanced Recovery After Aortic Surgery: A Single-Centre Experience“, Supervisor: Prof. E. Civilini
17/03/2020	**License to practice medicine, University of Milan (Italy)**
07/09/2020	**Recognition of qualifications to practice medicine in Germany**
01/10/2020 – present	**Trainee in vascular surgery, University Heart and Vascular Center Hamburg-Eppendorf (Germany)**

PUBLICATIONS AND ONGOING PROJECTS

1. Zhao Y, Xie B, Liu Q, et al. Endovascular Treatment of Post-traumatic Superior Mesenteric Arteriovenous Fistula: A Case Report. Ann Vasc Surg. 2018;50:297.e9-297.e13. doi:10.1016/j.avsg.2017.12.022.
2. Rossi M, Meggendorfer M, Zampini M, et al. Clinical Relevance of Clonal Hematopoiesis in the Oldest-Old Population: Analysis of the “Health and Anemia” Study. Blood. 2018;132(Suppl 1):750. doi:10.1182/blood-2018-99-114717.
3. Malik K, Poletto GL, Zhao Y, et al. Unconventional Endovascular Access for Symptomatic Thoracic Aortic Ulcer with Infrarenal Aortic Occlusion-A Case Report. Ann Vasc Surg. 2019;58:381.e1-381.e4. doi:10.1016/j.avsg.2018.10.049.
4. Zhang C, Li H, Guo X, et al. Clinical Diagnosis and Treatment of Internal Jugular Venous Aneurysms. Ann Vasc Surg. 2020;62:497.e7-497.e12. doi:10.1016/j.avsg.2019.06.022.
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10. Debus ES, Malik K, Kölbel T, et al. First-in-man Implantation of the Thoracoflo® Graft: a New Hybrid Device for Thoracoabdominal Aortic Repair – submitted for publication
11. Malik KD, Panuccio G, Kölbel T. Physician-modified iliac side branch device to prevent spinal cord ischemia in an urgent branched endovascular aortic repair – in preparation
12. Barbieri F, Malik K, Poletto GL, et al. Fast-Track Protocol for Carotid Endarterectomy – in preparation

CONGRESS PRESENTATIONS

20-23/09/2022	**ESVS 36th Annual Meeting** – Rome, Italy • Symposium Session Surgical Wounds - Enhanced Recovery: "Peri-Track in Vascular Surgery" – Malik K, Debus ES, Civilini E
16-17/09/2022	**27. Norddeutsche Gefäßtage** – Greifswald, Germany • Innovationen bei Rekonstruktionen – die Thoracoflo Prothese – Debus ED, Malik K, Kölbel T, Wipper S
28-29/09/2021	**ESVS 35th Hybrid Annual Meeting** – Rotterdam, The Netherlands • E-Poster Session, P-025: "Cost effectiveness of open repair of abdominal aortic aneurysms with a novel peri-op bundle" – Malik K, Vanni E, Malik K, Civilini E
21-23/10/2019	**SICVE 18th National Congress (Italian Society for Vascular and Endovascular Surgery)** – Florence, Italy • Under35 Grant Session (SICVE Premio): "ERAS protocol improves results in traditional repair of abdominal aortic aneurysms: a single-center experience" (in Italian) – Malik K, Poletto GL, Civilini E
13-15/12/2018	**8th International Congress of Aortic and Peripheral Surgery "HOW TO DO IT"** – San Raffaele Hospital; Milan, Italy • E-Poster Session: "ERAS in Open Aortic Repair Improves Clinical Outcomes: Single Center Experience on 471 Patients" – Malik K, Poletto GL, Civilini E
25-28/09/2018	**ESVS 32nd Annual Meeting** – Valencia, Spain • Scientific Session 8 - AAA, O-018: "Fast-track and Enhanced Recovery After Surgery (ERAS) in Open Aortic Surgery Improve Clinical Outcomes: A Single Centre Experience on 471 Consecutive Patients" – Poletto GL, Malik K, Musto L, Civilini E
22-25/09/2018	**CIRSE & IDEAS Annual Congress 2018** – Lisbon, Portugal • Poster Session, P-281: "Descending thoracic aortic ulcer in a patient with infrarenal aortic occlusion: how we managed a complex case" – Malik K, Poletto GL, Zhao Y, Civilini E
10/05/2018	**Annual Congress for General Practitioners** – Humanitas Hospital; Milan, Italy • "Our progress in understanding pathogenesis of abdominal aortic aneurysms" (in Italian) – Malik K

FURTHER TRAINING

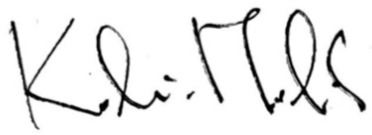
22-23/03/2022	Basic course for investigators/deputies and members of an investigator group in clinical trials under the Medicinal Products Act, Hamburg, Germany
08-09/06/2022	Basic course in radiation protection for doctors and medical physics experts, Hamburg, Germany
07-08/03/2021	24th European Vascular Course, Maastricht, The Netherlands
10-12/03/2019	23rd European Vascular Course, Maastricht, The Netherlands
13/12/2018	Hands-on Workshops: EVAR & open AAA-Repair, San Raffaele Hospital, Milan, Italy
05-06/10/2018	Theoretical-practical Course on Revascularisation Techniques of Lower Extremities, Humanitas Research Hospital, Milan, Italy
20-22/11/2017	Laparascopic Simulation Training, Humanitas Research Hospital, Milan, Italy

7. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.



Hamburg, 12.02.2023