THE ROLE OF MICROCIRCULATION IN THE PREVENTION AND TREATMENT OF POST-STERNOTOMY MEDIASTINITIS

PhD Thesis

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ABBREVIATIONS

AB	Antibiotic therapy
AVR/AVP	Aortic valve replacement/aortic valve plasty
BITA	Bilateral internal thoracic artery
BMI	Body mass index
BPMFP	Bilateral pectoral muscle flap plasty
C	Cardiac surgical classification
CABG	Coronary artery bypass grafting
CDC	Center for disease control and prevention
CI	Confedential intervallum
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
DSWI	Deep sternal wound infection
EuroSCORE II	European System for Cardiac Operative Risk Evaluation II
F	Female
FFP	Freshly frozen plasma
FOT	Failure of treatment
ICU	Intensive care unit
INPWT	Incisional negative pressure wound therapy

ITA	Internal thoracic artery
LITA	Left internal thoracic artery
M	Male
MRSA	Methicillin- resistant *Staphylococcus aureus*
MVR/MVP	Mitral valve replacement/ mitral valve plasty
NPWT	Negative pressure wound therapy
OPCABG	Off-pump coronary artery bypass grafting
P	Plastic surgical classification
PSM	Post- sternotomy mediastinitis
PSWI	Post- sternotomy wound infection
PVD	Peripheral vascular disease
RBC	Red blood cells
RITA	Right internal thoracic artery
SD	Standard deviation
SSI	Surgical Site infection
XIP	Xiphoid process

1. INTRODUCTION

Median sternotomy remains the standard surgical approach for cardiac surgery, despite the growing popularity of minimal access approaches (1-5). Median sternotomy has many advantages; it is simple, quick to perform, and provides wide access to almost all mediastinal structures. However, a major disadvantage of the median sternotomy incision is its suboptimal healing tendency.

Infection of sternal wounds remains a major surgical challenge that has a significant impact on morbidity, mortality, hospital costs, long-term survival, and patient's socio-psychological state (6-9).

The nomenclature and definition of sternal wound infections have not yet been standardized. Post-sternotomy wound infections (PSWIs), post-sternotomy mediastinitis (PSM), and deep sternal wound infections (DSWIs) are all used to refer to sternal infections involving the sternum and the underlying structures. However, it is important to distinguish superficial wound infections from deep wound infections. Superficial wound infections, with an incidence of 0.5- 8%, involve only the layers between the skin and the pectoral fascia, with the sternum remaining uninfected. These wounds are usually cured by local care and antibiotic therapy, and are associated with lower morbidity and mortality rates. Deep sternal wound infections are rare, with an incidence rate, depending on the definition used, of between 0.4% and 5%, and higher in-hospital mortality rate (7- 35%) (10).

In our daily practice, DSWIs are encountered and usually treated- in the early course- in cardiac surgical departments. However, due to the high rates of treatment failure, patients are referred to plastic surgical wards for final reconstruction. This might lead to a delay in final debridement and reconstruction, which might further increase morbidity and mortality rates (11-13). Determining which specialists should deal with the treatment of this devastating complication is controversial. It would be an unnecessary burden for a plastic surgeon to deal with every single wound. We propose that cardiac surgeons need to alter their approach to treating such wounds. Below we outline some of the important considerations that must be taken into account when planning treatments for DSWI.

1.1. Classifications of Sternal wound infections

Several attempts have been made to classify sternal wounds and to standardize how they should be treated. Some of these classifications are epidemiological, whereas others are based on clinical aspects. The available classifications are given Table 1.

Author	Year	P/C	Epidemiological/ Clinical	Aspects	Treatment suggestion	Microbiological aspect
CDC (14)	1988 1999	-	Epidemiological	-Time of infection -depth of wound - sternal involvement	-	+/-
Jones (15)	1997	P	Clinical	- Anatomic sites - presence of sepsis	-	-
El Oakley & Wright (16)	1996	C	Clinical	- Time of infection. - risk factors	-	-
Pairolero & Arnold (17)	1984	P	Clinical	- Time of infection	-	-
Greig (18)	2007	P	Clinical	- Localization of wound	+	-
Anger *et al* (19)	2013	P	Clinical	- Localization, depth, vertical extension of wound	+	-

Table 1. *Available classifications of sternal wound infections.*

There is no currently available classification that takes into account the microbiological environment of sternal wounds. Deep sternal wound infections can be clinically diagnosed based on symptoms and on the intraoperative view, even if the wound cultures are negative. So-called negative culture wounds are not always benign, and in some cases, total recovery is expected only after radical surgical debridement and reconstruction.

1.2. The pathophysiology of sternal wound infection

Three main factors are mandatory for optimal wound healing: infection control, stable osteosynthesis, and adequate perfusion.

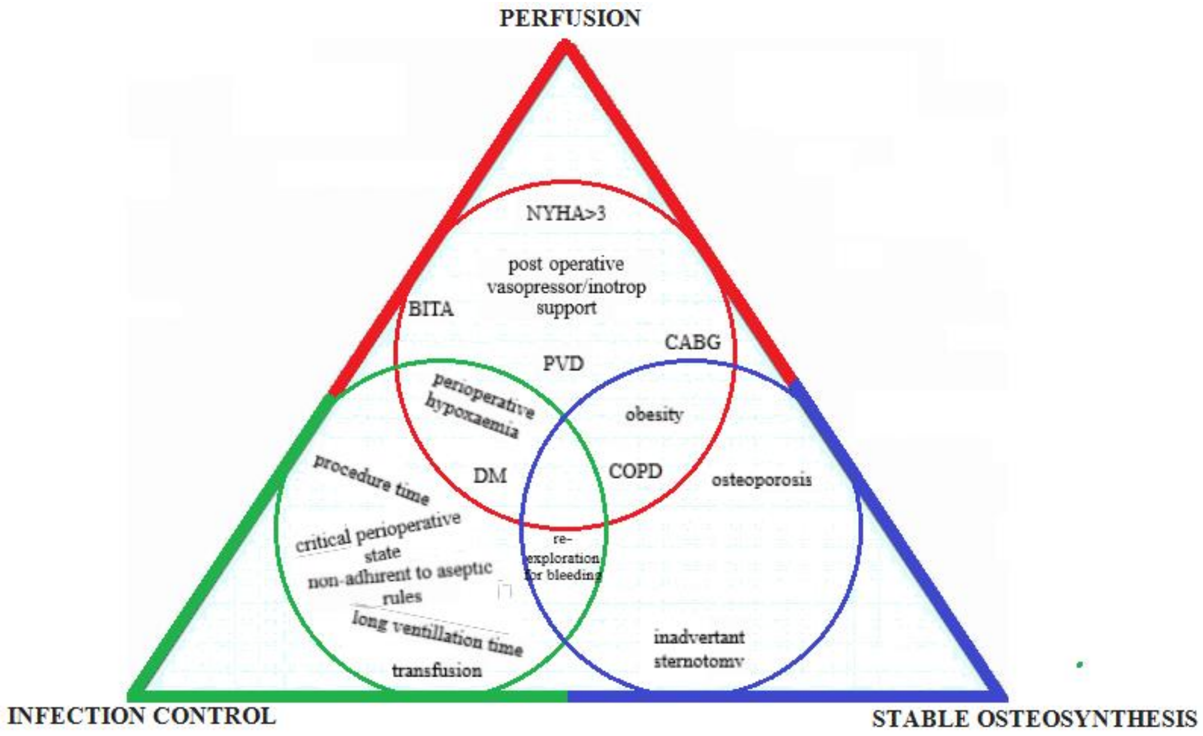


Figure 1.*The role of reported risk factors in the sternal wound healing triad.*

It is important to remember that reported risk factors predispose to sternal wound infections through breaking down one or more of the above- mentioned triad pillars (20-22).

1.3.The role of perfusion in prevention and treatment of DSWI

After the manifestation of DSWI, many cardiac surgeons put greater emphasis on the re-establishment of stable osteosynthesis, but little on the microcirculation conditions in the surgically reconstructed wounds. Perfusion is a cornerstone element in achieving uncompromised wound healing and increasing the success rates of surgical reconstruction. This understanding has led to the application of incisional negative pressure wound therapy on surgical incisions closed by primary intention, and the spread of using well- vascularised muscle flaps in the surgical treatment of sternal wounds infections (23, 24). In an animal study, *Hyunsuk et al* found that applying INPWT on closed surgical wounds with dead spaces facilitated the obliteration of dead spaces, improves perfusion, and increase collagen synthesis (25).

Patients undergoing open heart surgery can have various microcirculation states. Obese patients might suffer from poor perfusion of subcutaneous adipose layers with low levels of prophylactic antibiotics in this tissue (26). Smoking tobacco can impair the tissue microcirculation by increasing blood viscosity and altering the vasodilatory response (27), thus increasing the risk of DSWI. Capillary hyalinization and sclerosis are more prominent in diabetic microangiopathy (28), whereas capillary ischaemia and perfusion maldistribution are the main pathologies of peripheral vasculopathy (29, 30). These pathologies, alone or in combination, have an important impact on the wound healing process, as well as on the microcirculation of the surgically reconstructed wounds.

The left internal thoracic artery (ITA) is the best and most widely used graft in coronary artery bypass surgery. ITA can be harvested in a pedicled and skeletonized fashion. Many studies have reported at least a 20% reduction of sternal blood supply in the acute postoperative period if the ITA is harvested as a pedicled graft (31, 32). Three branches must be distinguished during the harvesting of ITA; *(i)* Sternal, running to the sternum, *(ii)* perforators, passing through intercostal muscles toward the pectoral muscle and develop collaterals with branches of the thoracoacromial artery, and *(iii)* intercostal, passing through the intercostal space and developing collaterals with the posterior intercostal branches derived from the descending aorta. Usually, beneath the sixth intercostal space, the ITA bifurcates into the musculophrenic and superior epigastric branches, which anastomose with the inferior epigastric artery. Preserving collaterals, as much as is possible, might contribute to improving the microvasculature of sternal wounds, which might lead to a reduced risk of infection.

1.4. New Approaches in prevention of DSWI

Recently, many new approaches have been reported to reduce the risk of DSWI. Those novel approaches reduce the risk of DSWI through one or more of the pillars involved in the sternal wound healing triad (33-41).

Infection Control	**Stable Osteosynthesis**	**Perfusion**
- Preoperative screening and decontamination of nasal carriage of *Staphylococcus aureus* - Gentamycin-collagen sponge - Vancomycin-coated paste	- Rigid sternal plating (bands or plates) - External chest support vest	- Incisional negative pressure wound therapy - Hyperbaric Oxigen therapy - Autologous platelet-rich plasma

Figure 2. *Novel approaches to reduce the risk of DSWI.*

1.5. The role of negative pressure wound therapy in prevention and treatment of sternal wound infections

In efforts to improve the microcirculation conditions in the sternal wounds, negative pressure wound therapy has become a standard approach in cardiac and plastic surgical practice. Two main indications can be formulated. The *traditional indication* lies in preconditioning infected sternal wounds to make them suitable for final surgical reconstruction. Under this indication negative pressure wound therapy is applied after thorough surgical debridement to improve the microcirculation conditions in the wounds, enhance the development of angiogenesis, and granulation tissue and serve as a bridge to final reconstruction (42, 43). In some superficial wounds, negative pressure wound therapy might serve as a bridge to wound healing. The *novel indication* involves applying negative pressure on wounds closed by primary intention. Incisional negative pressure wound therapy can be applied over primary closed or surgically reconstructed wounds to improve wound healing (44-46).

2. AIMS AND OBJECTIVES

The purpose of our recent work is to cover some of the gaps in cardiac surgeon’s knowledge in regards to prevention and treatment of deep sternal wound infections, emphasizing the role of the microcirculation aspects, stable biomechanics, and infection control.

2.1. Impact of INPWT on rates of failure of surgical reconstruction after DSWI

Dead spaces are usually developed as a consequence of radical surgical reconstruction of DSWI. Secretion accumulated in these dead spaces is usually drained out through Redon drains. A significant decrease in secretion volume and development of granulation tissue is mandatory in the obliteration of dead spaces. Here we examined the effect of applying INPWT in facilitating obliteration of dead spaces after surgical reconstruction.

We assumed that applying INPWT on surgically reconstructed infected wounds would improve regional perfusion especially when muscle flaps were used. We attempted to verify the impact of the application of INPWT on post-reconstructional sternal wounds in regards to rates of treatment failure and hospital stay.

2.2. Predictive factors of treatment failure of DSWI

While risk factors that predispose to the development of DSWI have been well documented, factors that predispose to failure of surgical treatment are less frequently mentioned. In an effort to improve success rates, we conducted a retrospective study to explore some of the factors that might predict treatment failure. We assumed that identifying factors that might contribute to treatment failure would help surgeons to make better surgical decision and thereby reduce the rate of treatment failure.

2.3. The role of sternal rewiring in surgical reconstruction of DSWI

In the cardiac surgical orthodoxy, sternal rewiring is thought to be mandatory to treat DSWI. Although radical surgical reconstruction is popular among plastic surgeons dealing with sternal wounds, adherence to sternal rewiring is a common surgical strategy in cardiac surgical departments. Based on our experience, we attempted to prove that radical surgical debridement, even at the expense of partial or total sternectomy, and improving the microcirculation state of these wounds, through mobilization of well vascularized pectoral muscle flaps, would be more expedient. We compared our results in patients, in which sternal rewiring was performed against those for which sternal rewiring was not performed.

2.4. The role of the XIP unit on the rates of DSWI

Considering the anatomical and embryological structure of the human sternum, and based on our observation that most DSWIs start with purulent discharge from the xiphoid region, we studied the role of preservation of the XIP unit in the pathophysiology of DSWI. Disruption of the XIP unit might contribute to regional perfusion defect, which might predispose to cartilage damage and necrosis subsequently followed by signs of infection and unstable osteosynthesis. First we introduced the concept of the "XIP unit". Then, we examined the effect of preservation of the XIP unit on the rates of DSWI.

2.5. Microbiological results in the classification of DSWI

Finally, we examined the impact of micrbiological culture results on patients survival rate.

Available clinical classifications of sternal wound infections do not include results of micrbiological cultures as a factor which might affect the surgical decision. We believe that microbiological cultures have a non-negligible impact on treatment success and survival rates after surgical reconstruction of sternal wound infections. We proposed a classification of sternal wounds based on microbiological cultures. Two classes are identified: culture- positive and cluture-negative DSWIs. Due to lack of general management protocols, we attempted to generate a treatment protocol by considering the results of microbiological cultures and the possibility of decontaminating wounds (important factors that should be considered together with anatomical site and extent and time of infection).

3. PATIENTS AND METHODS

Definitions and General Considerations

- The study was conducted in accordance with the Declaration of Helsinki. The institutional ethics committee approved the study (Approval No.: 10/2017).

- Failure of treatment (FOT) is defined as the need for surgical re-intervention or death during wound treatment. Diagnosis of DSWI was established based on the CDC criteria (Table 2).

1	Positive cultures from mediastinal tissue or fluid obtained during an invasive procedure.
2	Evidence of mediastinitis seen during an invasive procedure or histopathologic examination.
3	At least one of the following signs or symptoms: fever (> 38°C), chest pain, or sternal instability AND at least one of the following: - purulent discharge from the mediastinal area, - organisms cultured from blood or discharge from the mediastinal area, - and mediastinal widening on an imaging test.

Table 2. *CDC Criteria for the diagnosis of DSWI*

- Negative pressure wound therapy was applied using the Vivano System (Hartmann Ltd., Budapest, Hungary)
- Pairolero classification was based on the time manifestation of DSWI (Table 3).

Class	The manifestation of postoperative wound infection
I. Type	In the first postoperative week
II. Type	Between the second and sixth postoperative week
III. Type	After the sixth postoperative week (usually in the form of fistula or chronic osteomyelitis)

Table 3. *Pairolero classification of DSWI*

- Microbiological cultures from the wound discharge were obtained routinely regardless of the nature of the discharge (serosanguinous or purulent). All patients underwent the same perioperative antibiotic prophylaxis.
- sternal rewiring group, the sternum was rewired after debridement. Rewiring was performed using stainless steel wires, which were passed parasternally in a horizontal or horizontal and longitudinal manner, depending on the surgeon’s assessment.
- In the no sternal rewiring group, no sternal wires were used in the final reconstruction. The sternum was either resected or left mechanically unfixed (in chronic cases) until subsequent bilateral pectoral muscle flap advancement plasty was performed.
- Primary sternal wiring refers to the primary cardiac operation closure.
- XIP unit is the anatomical unit, which consists of the bony-cartilaginous anatomical XIP, its muscular attachments, the overlying skin, and the bifurcation of the ITA.
- XIP-sparing sternotomy is defined as midline sternotomy with the preservation of the XIP unit.
- Standard midline sternotomy is defined as midline sternotomy without the preservation of the XIP unit. Acut procedures were defined as procedures performed within 24 h of diagnosis. Obesity was defined as BMI> 30kg/m^2.

3.1. INPWT Study

In this study, we analyzed the data of 21 consecutive patients who developed DSWI after open heart surgery through a median sternotomy and underwent surgical reconstruction. After surgical reconstruction of the wounds, we applied INPWT together with Redon drains in ten patients (INPWT + Redon group). In 11 patients, INPWT was not applied (Redon only group).

In both groups, Redon drains were removed when daily secretion dropped below 30 ml. Incisional negative pressure over the wound was applied for 10 days (Figure 3).

Figure 3. *INPWT dressing set and a vacuum generator.*

We examined

the time between introduction and removal of Redon drains,

hospital stay, and

the rate of treatment failure.

The follow-up period was 6 months.

3.2. Predictive factors of treatment failure

In this study, data from 3177 consecutive patients who underwent median sternotomy were retrospectively analyzed and among this cohort, DSWI was diagnosed in 60 patients (1.9%). First, those patients who developed DSWI were divided into three subgroups according to the Pairolero classification (Table 3): *Group I*, infections presented between the day of operation and the sixth postoperative day (day 0-6); *Group II*, infections presented between the seventh and 30th day postoperatively (day 7-30); and *Group III*: infections presented after the 30th postoperative day (after day 30).

I. Group	n = 18	30%
II. Group	n = 32	53.3%
III. Group	n = 10	16.7%
Total	n = 60	100%

Table 4. *Classification of the study's patient according to the Pairolero classification.*

Other factors that might contribute to the development of FOT, including risk factors (sex, age, body mass index, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, type and urgency of cardiac operation, use of internal mammary artery, and transfusion), nature of surgical intervention, and microbiological culture were all identified and statistically analyzed.

The first surgical reconstruction was performed by conventional surgical procedures in all patients (debridement and application of negative pressure wound therapy, mediastinal irrigation, sternal rewiring and closure over Redon drainage). Patients in whom the first surgical reconstruction failed underwent a second reconstruction attempt (n =29). We divided these patients into two subgroups depending on the radical nature of the second surgical intervention. The more radical surgical intervention included hemi- or total sternectomy, resection of the cartilaginous part of the ribs, and closure with unilateral or bilateral pectoral muscle, advancement or turnover, flaps, (R group n =11). Eighteen patients underwent another conventional reintervention (C group n = 18).

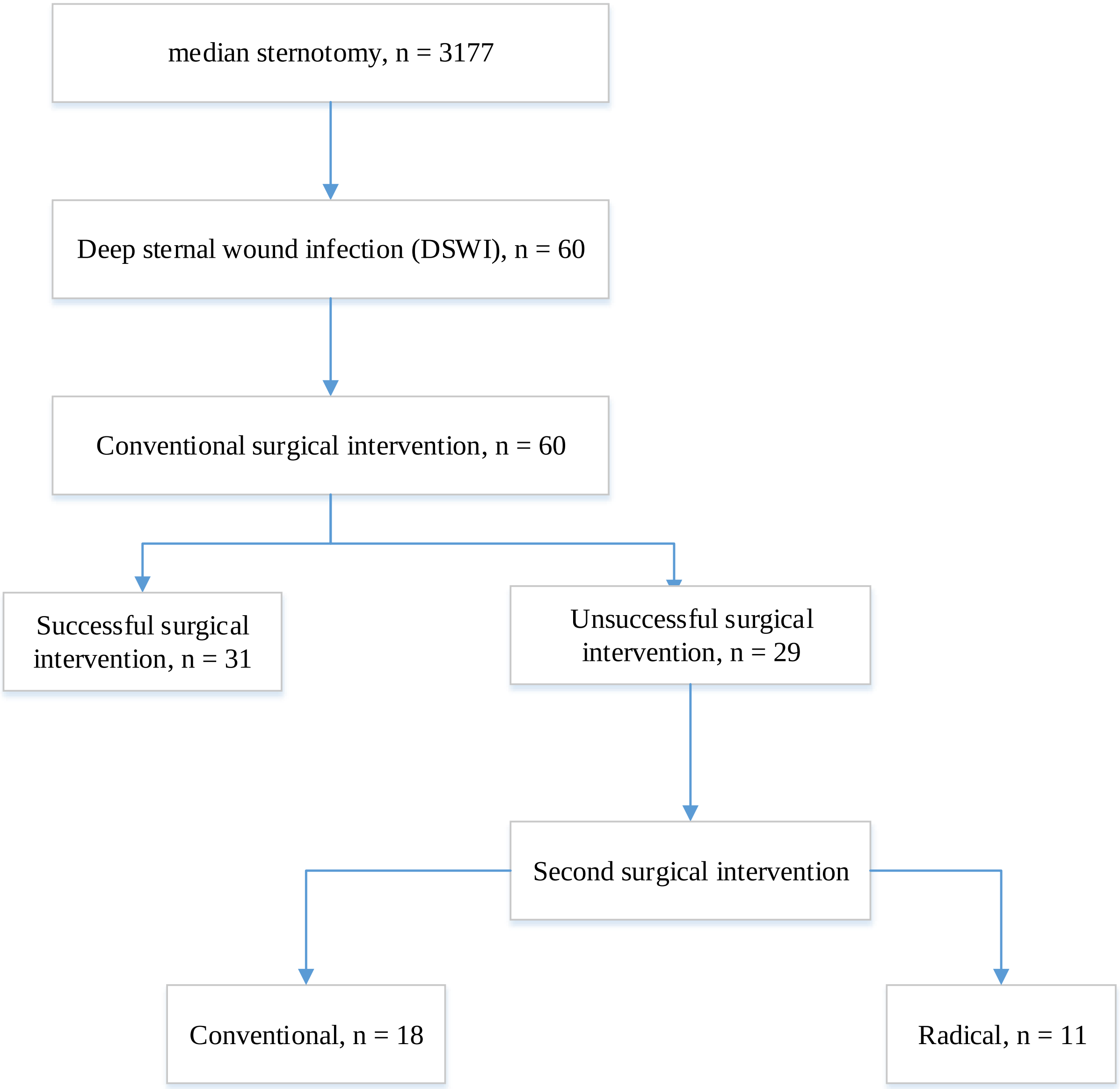


Figure 4. *Surgical intervention in the study groups.*

3.3. The role of sternal rewiring in surgical reconstruction of DSWI

After exlusion of four patients from the 3.2 study, who died before final surgical reconstruction, data from the remaining 56 patients, who developed DSWI and underwent final surgical reconstruction were analyzed. Based on the surgeon’s decision, patients were divided into two groups: patients where sternal rewiring was performed (sternal rewiring group), and patients where other interventions, but no sternal rewiring (no sternal rewiring group), were performed. Other interventions included sternal debridement without rewiring, hemi- or total sternal resection, and bilateral pectoral muscle flap plasty in combination with Redon drainage.

We examined:

the need for **readmission** or **death within 90 days**, and

length of hospital stay.

The follow- up period was 12 months.

Figures 5- 7 summarizes the various surgical procedures performed in the two groups.

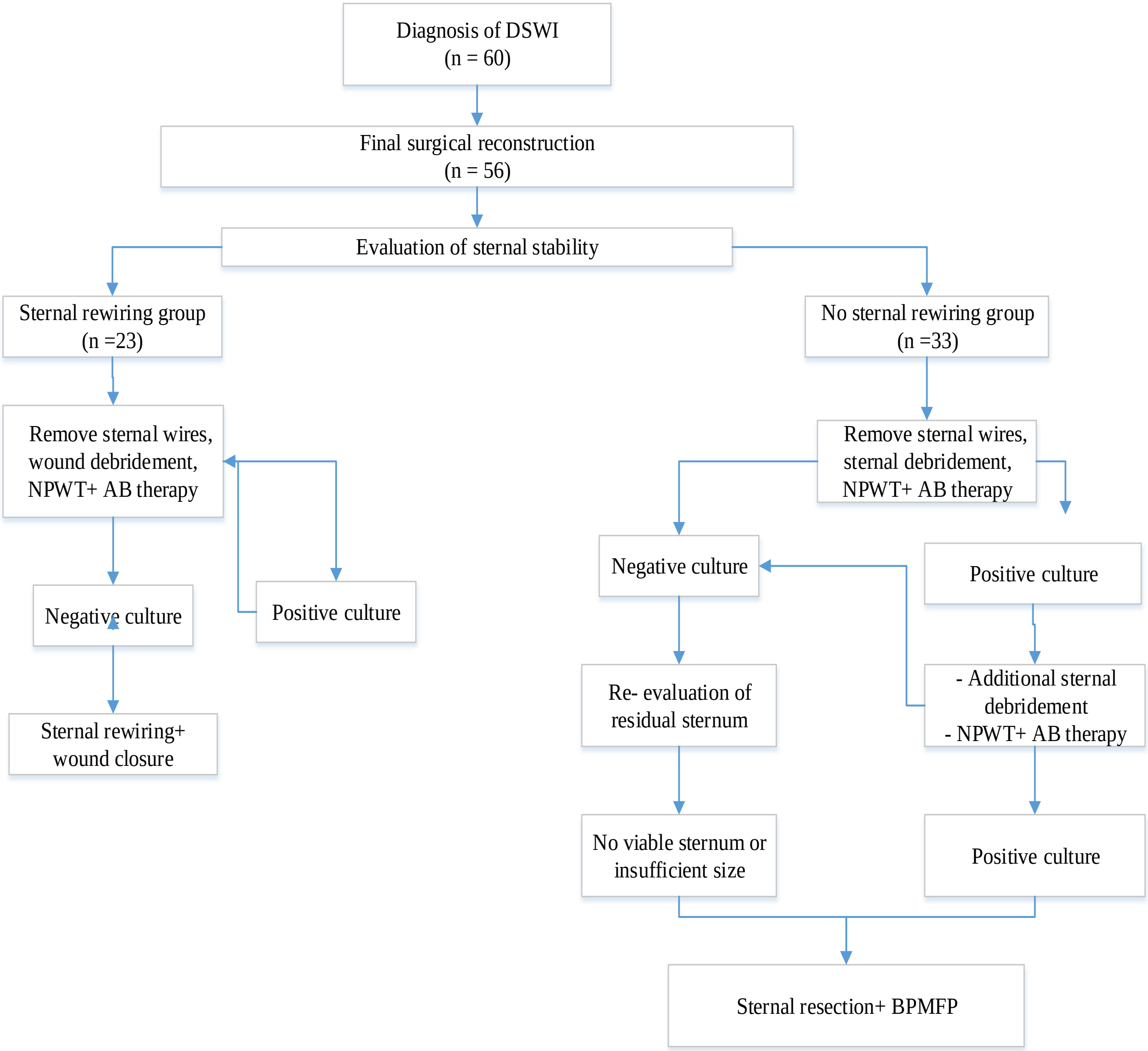


Figure 5. *Surgical management of deep sternal wound infections in the sternal rewiring and no sternal rewiring groups.*

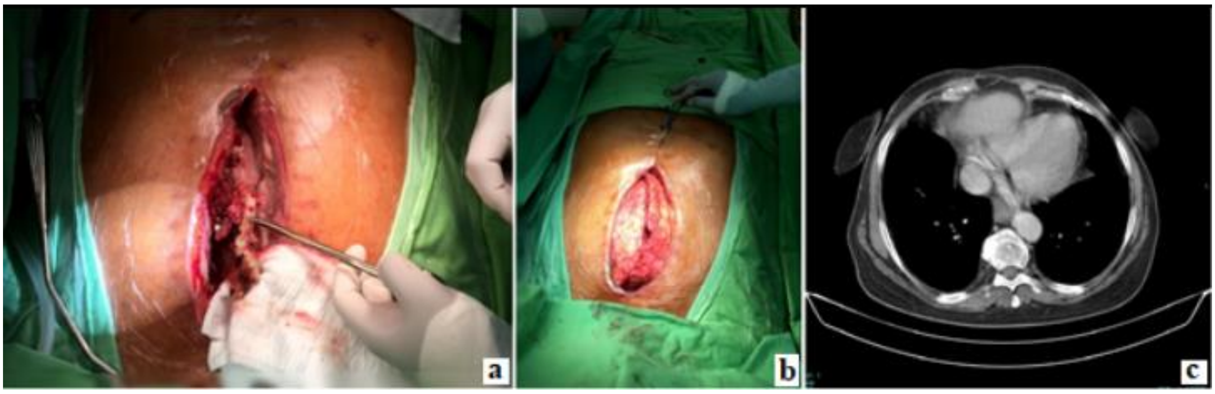


Figure 6. *Surgical treatment of deep sternal wound infection with nonviable sternal fragments: a) Total sternectomy, b) bilateral advancement pectoral flap plasty to cover the defect, and c) computer tomographic image six months after final surgical reconstruction. The thoracic cage was stable and the patient was symptom-free.*

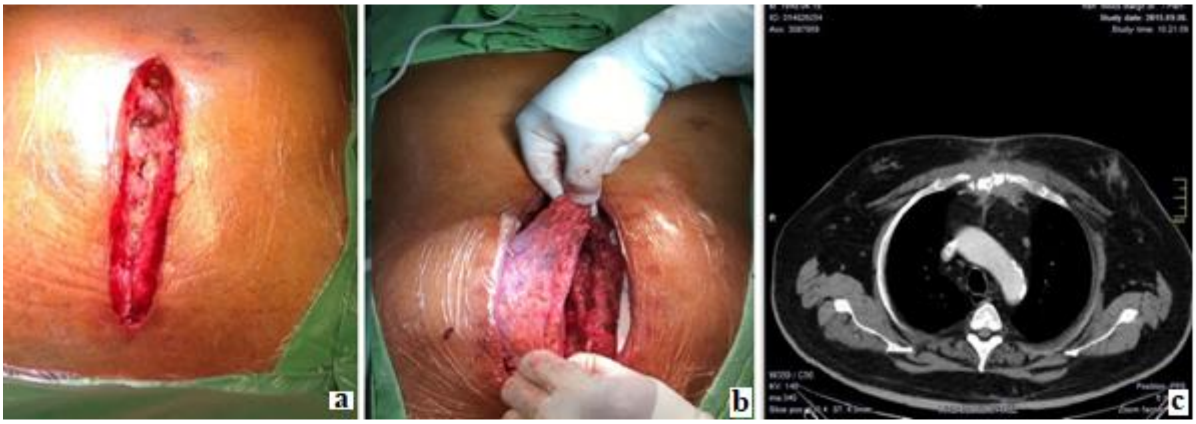


Figure 7. *Surgical treatment of deep sternal wound infection: a) Granulation tissue fixes the viable sternal halves in place after wire removal and extensive debridement, b) bilateral pectoral muscle flap plasty without sternal rewiring, and c) computer tomographic image six months after final surgical reconstruction showing well-vascularized tissue covering the mediastinum. The patient was symptom-free.*

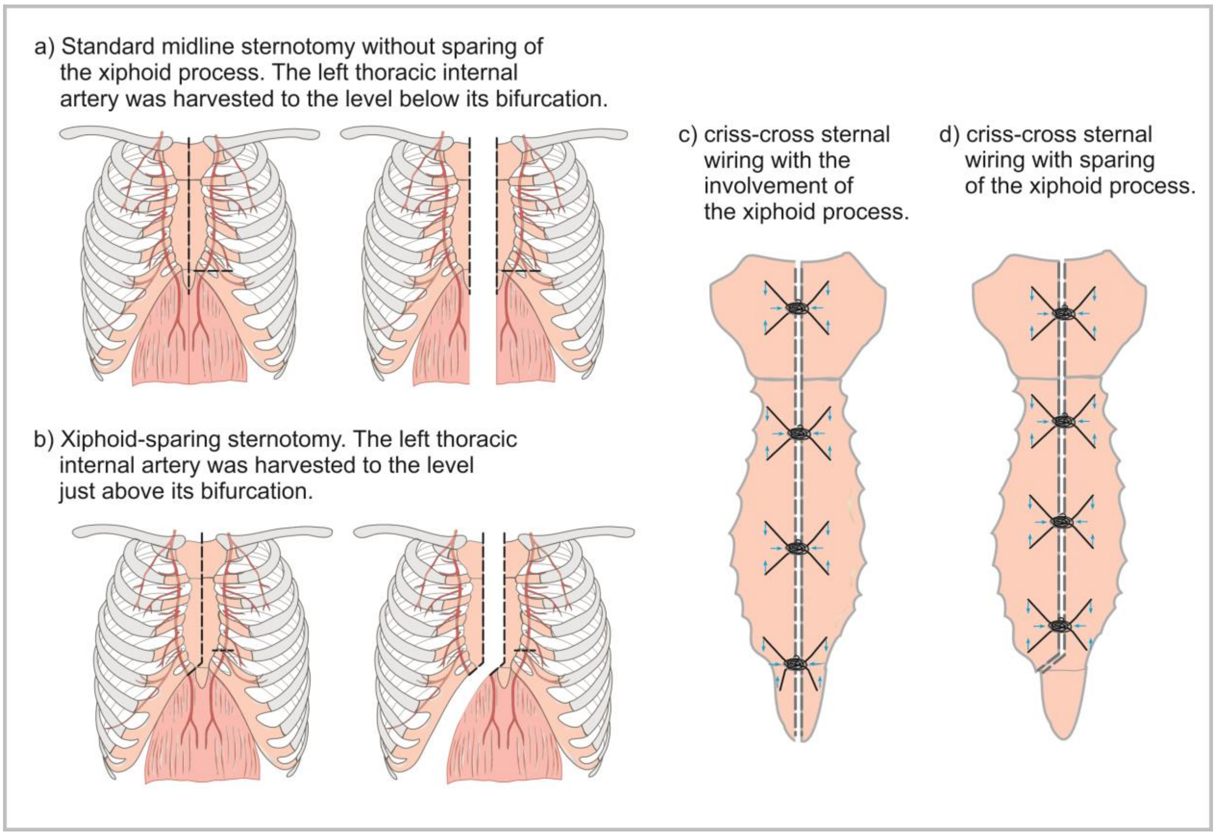
3.4. The role of XIP unit in reducing rates of DSWI

We conducted a cohort study to estimate the impact of the preservation of XIP unit integrity on the development of DSWI; data from 948 patients, who underwent coronary bypass grafting with the left internal thoracic artery, in the period between January 2012 and May 2017 were prospectively collected and retrospectively analyzed. We excluded all patients who underwent harvesting of the right or bilateral internal thoracic artery, minimally invasive direct coronary artery bypass grafting, coronary revascularization alone with venous conduits, surgeries other than coronary artery bypass grafting, and re-do operations. Patients were divided into two groups: Group I *(XIP group*, n =250), and Group II *(non-XIP group*, n =698).

We examined:

the impact of preservation of the XIP unit on the **rates of DSWI**.

Figures 8 and 9 show the surgical techniques.



a) Standard midline sternotomy without sparing of the xiphoid process. The left thoracic internal artery was harvested to the level below its bifurcation.

b) Xiphoid-sparing sternotomy. The left thoracic internal artery was harvested to the level just above its bifurcation.

c) criss-cross sternal wiring with the involvement of the xiphoid process.

d) criss-cross sternal wiring with sparing of the xiphoid process.

Figure 8. *Surgical techniques in the XIP and non-XIP sparing median sternotomy groups.*

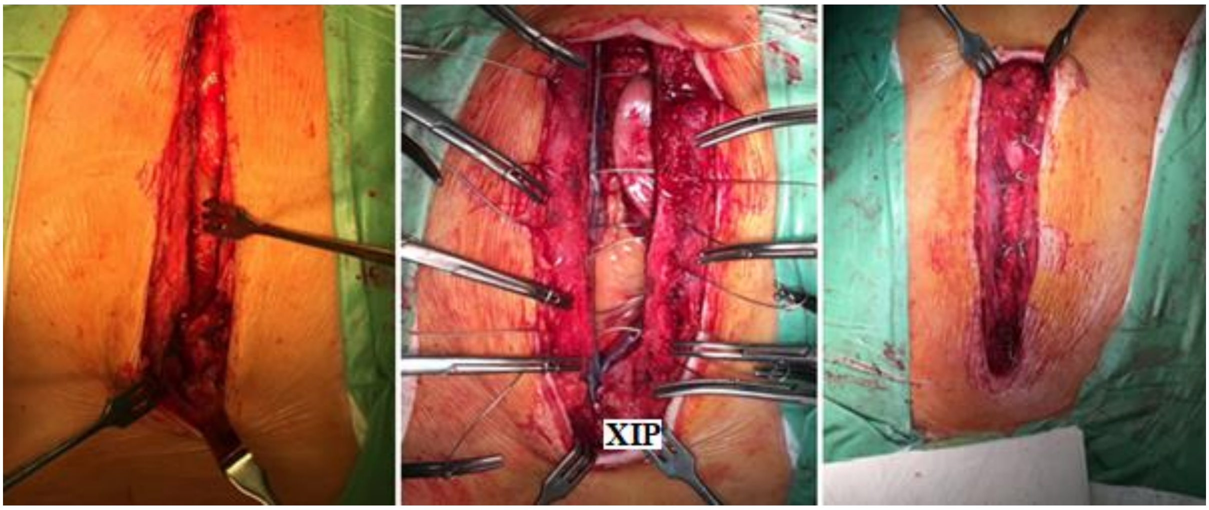


Figure 9. *The intraoperative view.*

3.5. Microbiological classification of DSWI

We performed a retrospective analysis of data from 92 consecutive patients who developed DSWI based on clinical, biomarker, and intraoperative view, independently of the results of the microbiological culture (Figure 10).

CLINICAL DIAGNOSIS of DSWI

Signs and symptoms	***Inflammatory biomarkers***	***Intraoperative view***
- **Pain**: sudden appearance, over the sternum, may radiate to the shoulders, - **Fever** - **Crepitation** over the sternum - **Wound hyperemia, edema** - **Purulent discharge**	- Elevated **CRP** - **Leukocytosis**	- **Loosened sternal wires** with seemingly infected wires channels - **Sternal dehiscence** with mediastinal purulent discharge - Development of **biofilms** around wires and destructed bone

Figure 10. *Pillars of clinical diagnosis of DSWI.*

Based on the intraoperative view, sternal involvement was documented in all cases and surgical reconstruction, including sternal rewiring, hemi- or total sternectomy and BPMFP, was performed in all patients. Microbiological sampling was performed in every case after the manifestation of wound discharge. Patients with superficial infections and no sternal involvement were not included in this analysis, even if the results of microbiological culture were positive. Based on results of microbiological cultures, patients in this study were divided into two groups: those with positive- culture wounds including patients with clinically infected sternal wounds and positive microbiological culture; and those with negative-culture wounds including patients with clinically infected sternal wounds but negative microbiological culture. Microbiological sampling was performed using standard microbiological procedures.

We examined the **90-days**, **1-year**, and **2-years survival rates** in both groups.

4. STATISTICAL ANALYSIS

Statistical analysis used IBM SPSS software (Version 20, IBM Corp., released 2011. IBM)
For the comparison of data, Chi-squared and Student’s *t*-tests were applied. P values less than 0.05 were considered to indicate statistically significant differences. Categorical variables were presented as frequencies and percentages and compared between groups using Chi-squared or Fisher’s exact tests.
In **Section 3.1.**, if the test of equality of variances (Levene test) was significant, the Kruskal–Wallis test was used. The results are displayed in the form of percentage, mean ± standard deviation or box-plot, where medians in the 25–75% and 2·5–7·5% percentile ranges were depicted.

In **Sections 3.2. and 3.3.**, continuous variables were expressed as medians and interquartile ranges or means and standard deviations. Kolmogorov-Smirnov test was used to check the normal distribution and subsequently student's t or Mann-Whitney U tests were used where appropriate. Box plot graphics were used to illustrate comparisons between subgroups, displaying a statistical summary of the median, quartiles, 25–75% and 2.5–7.5% percentile ranges, and extreme values.

In **Section 3.4.**, the differences in the baseline and operative characteristics of patients included in the two groups were compared using the independent sample t-test for continuous variables and the Chi-square test for categorical variables. To reduce the impact of treatment selection bias and potential confounding, we balanced the distribution of covariates between the XIP-sparing and non-XIP subgroups with the inverse probability of treatment weighting. Using XIP unit sparing as a dependent variable, related outcomes and confounding (related to treatment) covariates [diabetes mellitus, chronic obstructive pulmonary disease, European System for Cardiac Operative Risk Evaluation (EuroSCORE II), operative time, red blood cells, and freshly frozen plasma transfusion] were included in the binary logistic regression analysis to compute the propensity score. The model was well calibrated according to the Hosmer-Lemeshow test ($p = 0.371$). During the calculation of weighted samples, the weight for patients in the XIP-sparing subgroup was the inverse propensity score and the weight for patients in the non-XIP subgroup was the inverse of 1- propensity score. The mean weight was 1.91 ± 1.27. For adjusting the inflating effect of the sample size to original sample size, a robust method, the Generalized Linear Model was applied in order to calculate variance and covariance in the weighted sample. To estimate the treatment effect of XIP sparing on the development of DSWI, a binary logistic model was used.

In **Section 3.5.**, Kaplan-Meier estimates were used to calculate survival curves. Any differences between curves in 90-days, 1-year, and 2-years survival rates were explored using log-rank chi-square (Mantel-Cox) tests.

5. RESULTS

5.1. INPWT Study

The baseline characteristics of patients in both groups (INPWT + Redon vs. Redon only) are given in Table 5a.

Patients' characteristics	**INPWT + Redon (%; mean ± SD; median) (n = 10)**	**Redon only (%; mean ± SD; median) (n = 11)**	**p value**
Age (years)	61.2 ± 8.7	63.6 ± 8.6	0.562
Sex (M/F)	8/2	6/5	0.217
Obesity (%)	60.0	27.7	0.130
DM (%)	70.0	54.5	0.466
COPD (%)	50.0	45.5	0.835
PVD (%)	30.0	18.8	0.525
acute procedure (%)	20.0	36.4	0.407
CABG (%)	90.0	90.9	0.943
EuroSCORE II	2.7 ± 2.2	2.8 ± 2.5	0.169
ITA (%)	80.0	72.7	0.696
procedure time (min.)	213 ± 111	183 ± 51	0.429
RBC transfusion (U)	3.2 ± 4.7	1.3 ± 1.4	0.241

Table 5a. *Baseline characteristics of patients in both groups (INPWT + Redon vs. Redon only).*

Patients' characteristics	INPWT + Redon (%; mean ± SD; median) (n = 10)	Redon only (%; mean ± SD; median) (n = 11)	p value
FOT (%)	10	45.5	0.72
Redon drainage time (days)	6.9 ± 5.2	13 ± 11.6	0.122
Hospitalisation time (days)	22.5	95,7	0.001

Table 5b. *Results of the examined parameters in both groups (INPWT + Redon vs. Redon only).*

There was no difference between the two groups regarding age, sex or risk factors. There was no statistically significant difference between the duration of Redon drainage and the rate of treatment failure. Nevertheless, these two parameters were lower in the INPWT+Redon group than in the Redon only group. Hospitalization time was significantly shorter in the INPWT+redon group than in the Redon only group.

Only one patient needed surgical reintervention in the INPWT+redon group compared to five patients in the Redon only group. Two patients died during their hospital stay in the Redon only group. In the follow-up period, survival was 100% in the INPWT+Redon group, and computed tomography scans revealed no signs of inflammation of the mediastinal structures.

5.2. Predictive factors of FOT

Out of 60 patients, the FOT criteria were reached in 29 (48.3%). According to the Pairolero classification, FOT occured in 27.8% of Group I, 53.1% of Group II, and 70% of Group III, P= 0.005).

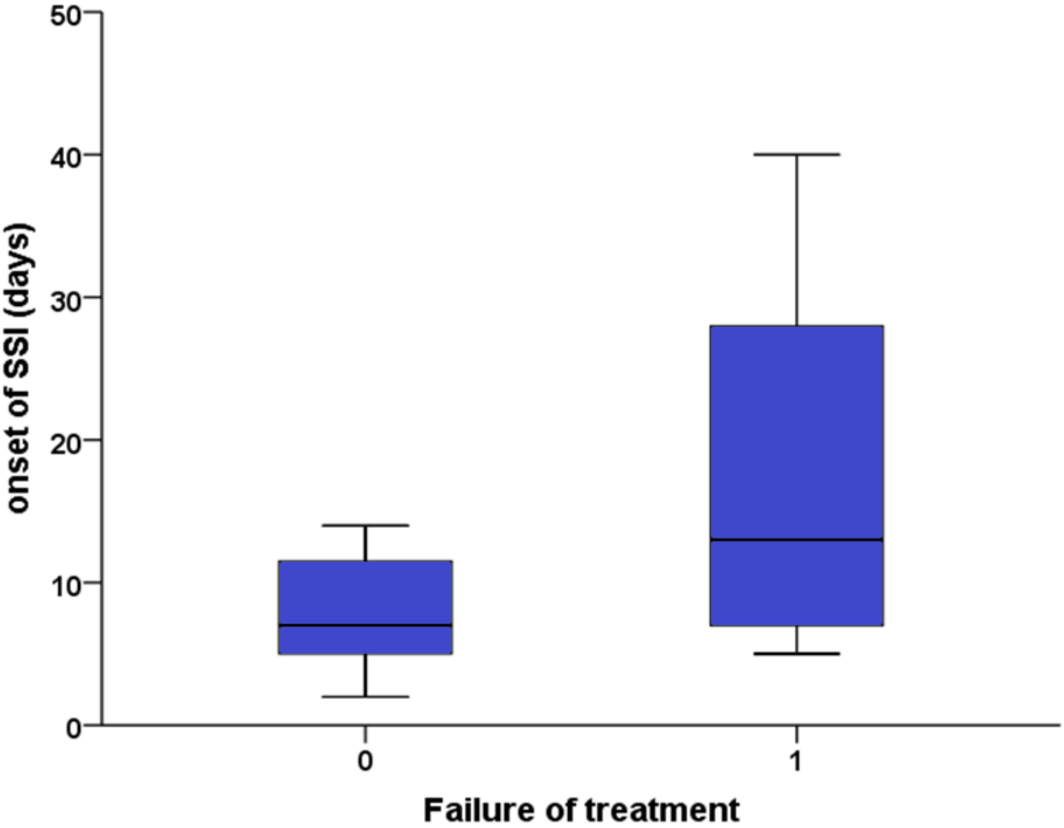


Figure 11. *The time onset of SSI and FOT after the first reconstruction. (Mann Whitney test, p = 0,005).*

Treatment failure was more frequent if wound cultures were positive at the time of reconstruction than when cultures were negative (69.0% vs. 22.6%, p <0.001).

Peripheral vascular disease was the only risk factor, among those included in the study, that significantly contributed to FOT (Table 6).

Patients' characteristics	**FOT** **(n = 29)** **(%; mean ± SD)**	**No FOT** **(n = 31)** **(%; mean ± SD)**	**p value**
Age	63.6 ± 7.6	64.3 ± 6.8	0.732
Sex (M/F)	19/10	25/6	0.185
Obesity (%)	34.5	16.1	0.101
DM (%)	62.1	45.2	0.190
COPD (%)	51.7	29.0	0.073
PVD (%)	44.8	9.7	0.002
Acute procedure (%)	17.9	29.0	0.134
CABG (%)	82.8	80.6	0.833
EuroSCORE II	1.9 ± 1.7	2.1 ± 1.6	0.114
ITA (%)	69.0	74.2	0.653
RBC transfusion	2.14 ± 3.4	1.6 ± 2.1	0.473

Table 6. *The contribution of risk factors to the development of FOT.*

Success rates in the radical surgery group were significantly higher than in the conventional group (88.1 vs. 11.1%, p <0.001), (Figure 9). In this retrospective study, five patients died (12%). Mortality was higher in the conventional group (5/18 [27.6%] vs. 0/11 [0%], p = 0.002).

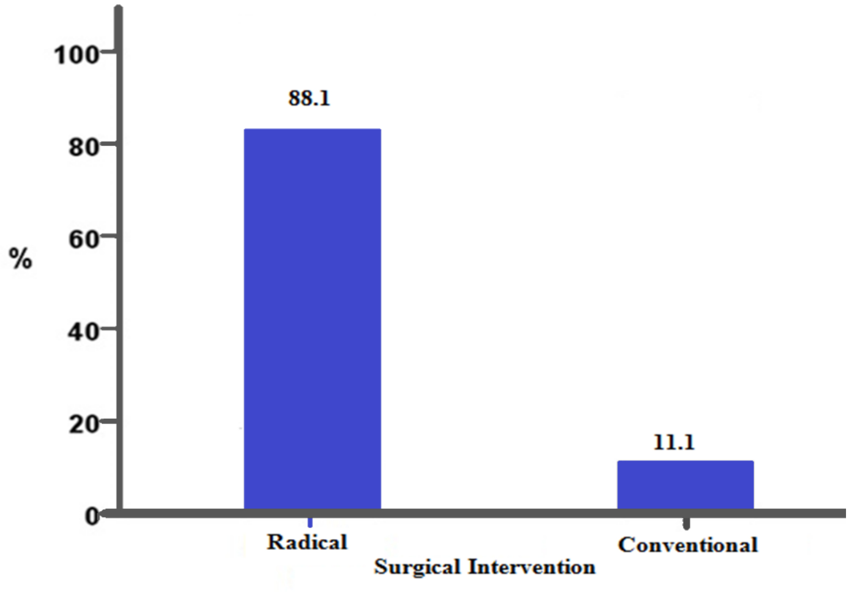
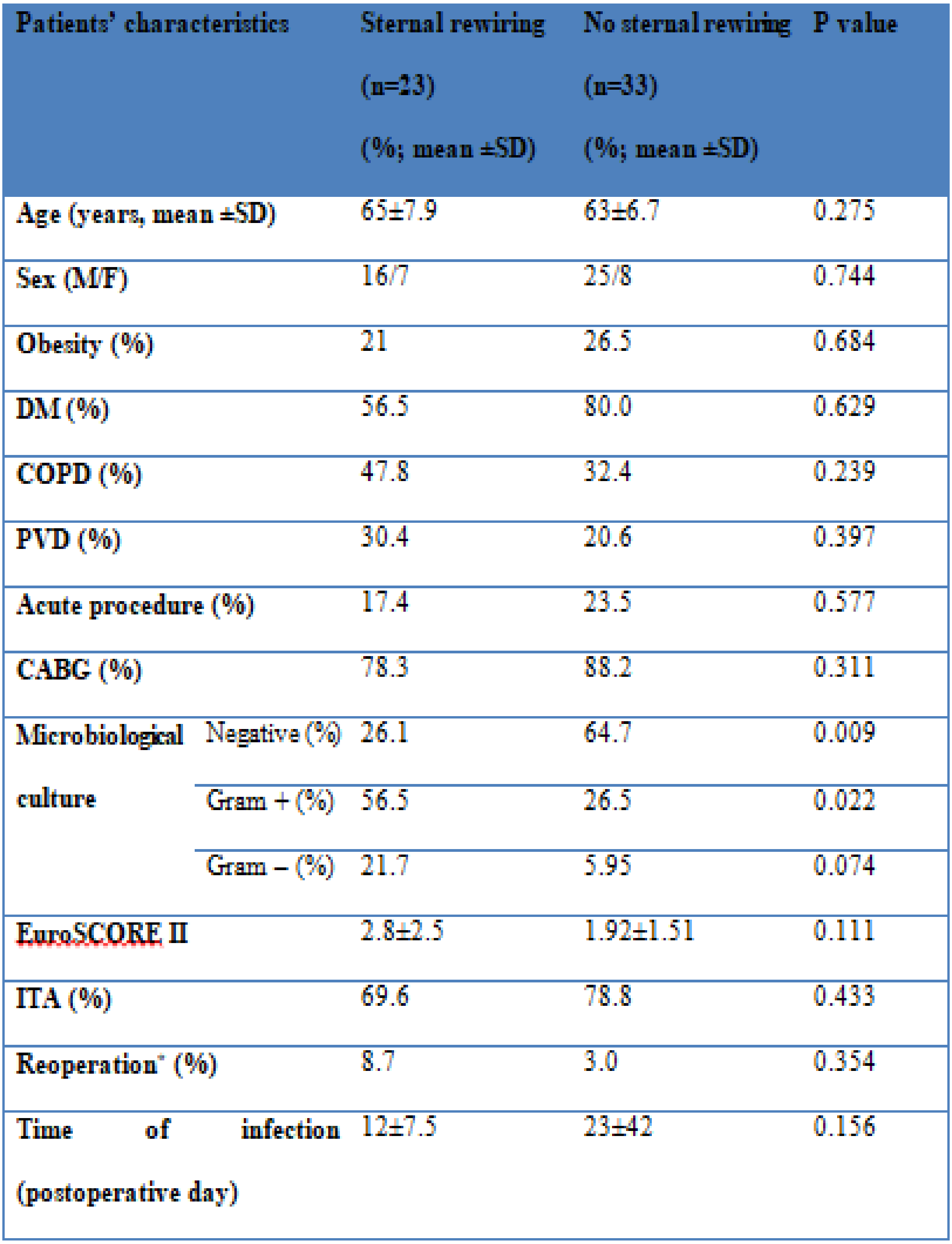


Figure 12. Success rates after radical and conventional surgical treatment.

5.3. The role of sternal rewiring in the development of FOT

The rate of readmission was higher in the sternal rewiring group than in the no sternal rewiring group (63.6% vs. 14.7%, respectively; P <0.001). Readmissions were usually due to early excessive wound discharge, symptomatic sternal instability, or chronic fistula. The overall 90-day mortality rate was 8.9% (5/56; sternal rewiring, 21.7% [5/23] vs. no sternal rewiring, 0%, [0/33]; p = 0.030). No additional deaths occurred during the 12-month follow-up period. Further, the median length of hospitalization was significantly longer in the sternal rewiring group than in the no sternal rewiring group (51 vs. 30 days; p = 0.006).



Patients' characteristics		Sternal rewiring (n=23) (%; mean ±SD)	No sternal rewiring (n=33) (%; mean ±SD)	P value
Age (years, mean ±SD)		65±7.9	63±6.7	0.275
Sex (M/F)		16/7	25/8	0.744
Obesity (%)		21	26.5	0.684
DM (%)		56.5	80.0	0.629
COPD (%)		47.8	32.4	0.239
PVD (%)		30.4	20.6	0.397
Acute procedure (%)		17.4	23.5	0.577
CABG (%)		78.3	88.2	0.311
Microbiological culture	Negative (%)	26.1	64.7	0.009
	Gram + (%)	56.5	26.5	0.022
	Gram – (%)	21.7	5.95	0.074
EuroSCORE II		2.8±2.5	1.92±1.51	0.111
ITA (%)		69.6	78.8	0.433
Reoperation* (%)		8.7	3.0	0.354
Time of infection (postoperative day)		12±7.5	23±42	0.156

Table 7. *Baseline data of patients with DSWIs in the sternal rewirinig and no sternal rewiring groups.*not due to wound complications.*

5.4. The role of preservation of the XIP unit in reducing the risk of DSWI

DSWI rate in the entire study population was 4.7%. The DSWI rates in the XIP-sparing and non-XIP sparing groups were 0.8% and 6.1%, respectively, ($p = 0.001$).

Baseline and operative characteristics and clinical outcome data of the patients in the XIP-sparing and non-XIP subgroups groups are shown in Table 8.

Patients’ characteristics	XIP-sparing (n = 250) (%; mean ± SD)	non-XIP (n = 698) (%;mean±SD)	p-value
Age (years)	63.8 ± 8.8	64.6 ± 8.2	0.203
Sex (M, %)	78.8	76.8	0.515
Obesity (%)	19.2	16.8	0.383
DM (%)	40.4	41.4	0.782
COPD (%)	12.8	11.5	0.574
PVD (%)	27.6	23.6	0.213
OPCABG (%)	71.2	69.5	0.612
On-pump procedures (%)	11.2	9.0	0.317
EuroSCORE II	1.7 ± 1.2	2.1 ± 2.2	0.001
procedure time (min.)	152 ± 77	195 ± 71	< 0.001
RBC transfusion (U)	1.1 ± 1.9	1.6 ± 2.6	0.003
FFP transfusion (U)	0.1 ± 0.6	0.3 ± 1.1	0.010
Ventilation time (hours)	8.8 ± 17	10.1 ± 25	0.255
ICU time (hours)	56 ± 49	57 ± 44	0.739

Table 8. *Baseline data of the patients in the XIP-sparing and non-XIP subgroups groups.*

Based on the binary logistic model using inverse propensity score-weighted samples, the XIP-sparing approach had a significant therapeutic impact on DSWI rates after coronary artery surgery compared to conventional sternotomy.

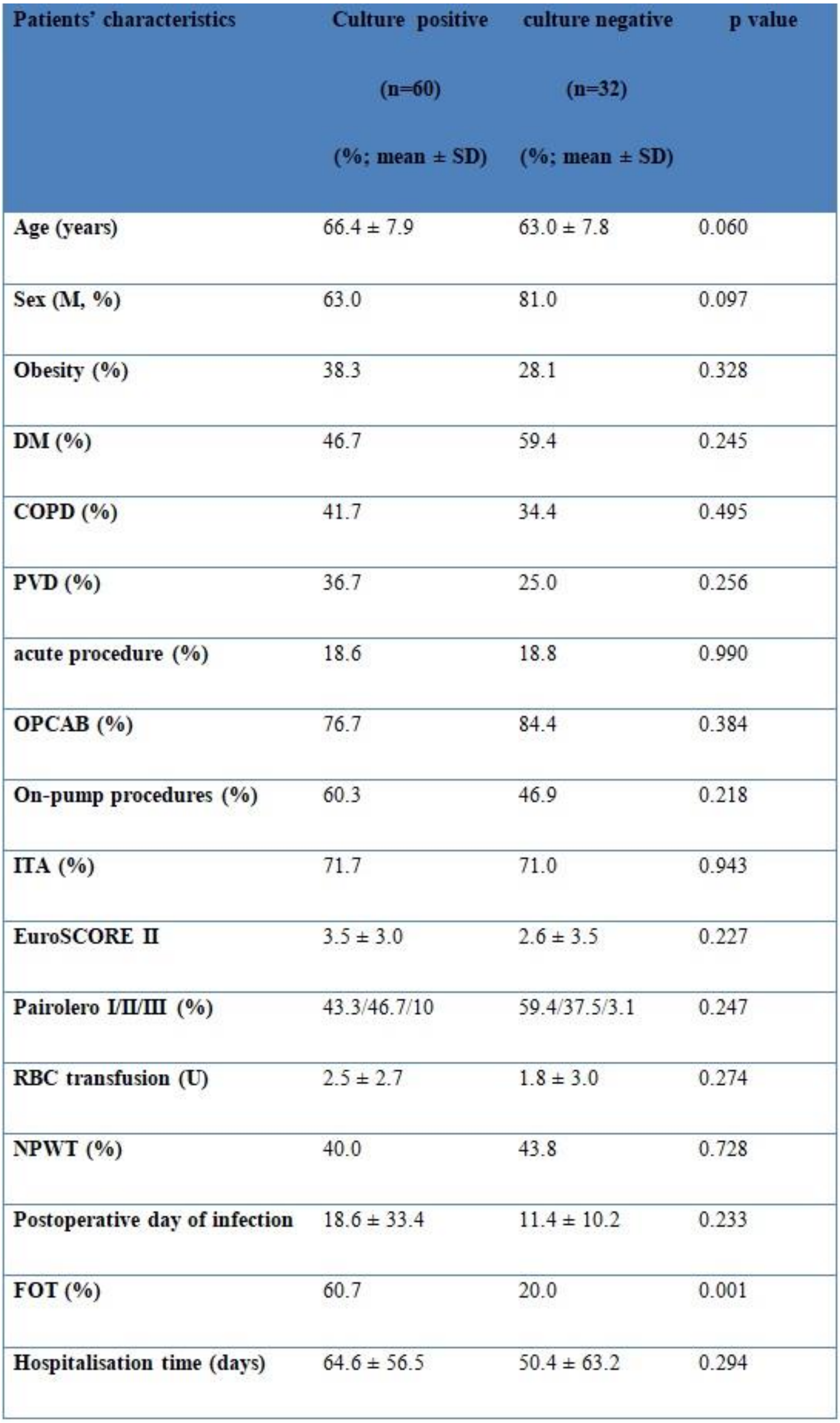
The adjusted odds ratio of DSWI in the XIP sparing-group was 0.087 (95% CI: 0.020–0.381, p = 0.001) (Table 9).

Parameter	**B**	**SE**	**95% CI**		**Wald**	**Sig.**	**Exp (B)**	**95% CI**	
(Intercept)	-2.559	0.2502	-3.049	-2.068	104.6	<0.001	0.077	0.047	0.126
XIP= 1	-2.442	0.7535	-3.919	-0.965	10.502	0.001	0.087	0.020	0.381

Table 9. *Effect of sparing the XIP unit on DSWI rates (dependent variable) after coronary bypass surgery. Results of the binary logistic model.*

5.5. Impact of results of microbiological cultures on survival rates after DSWI

Table 10 shows the baseline data of patients in the positive-culture wounds and negative-culture wounds groups.



Patients' characteristics	Culture positive (n=60) (%; mean ± SD)	culture negative (n=32) (%; mean ± SD)	p value
Age (years)	66.4 ± 7.9	63.0 ± 7.8	0.060
Sex (M, %)	63.0	81.0	0.097
Obesity (%)	38.3	28.1	0.328
DM (%)	46.7	59.4	0.245
COPD (%)	41.7	34.4	0.495
PVD (%)	36.7	25.0	0.256
acute procedure (%)	18.6	18.8	0.990
OPCAB (%)	76.7	84.4	0.384
On-pump procedures (%)	60.3	46.9	0.218
ITA (%)	71.7	71.0	0.943
EuroSCORE II	3.5 ± 3.0	2.6 ± 3.5	0.227
Pairolero I/II/III (%)	43.3/46.7/10	59.4/37.5/3.1	0.247
RBC transfusion (U)	2.5 ± 2.7	1.8 ± 3.0	0.274
NPWT (%)	40.0	43.8	0.728
Postoperative day of infection	18.6 ± 33.4	11.4 ± 10.2	0.233
FOT (%)	60.7	20.0	0.001
Hospitalisation time (days)	64.6 ± 56.5	50.4 ± 63.2	0.294

Table 10. *Baseline data of patients in the positive-culture wounds and negative-culture wounds groups.*

Consistent with our findings in Section 3.2, in this study, FOT was more frequent when wound cultures were positive. Nevertheless, the FOT rate in the negative-culture wounds group was 20%, which might be due to incomplete surgical debridement. Survival rates were significantly better at 90 days, 1 year, and 2 years in the negative-culture wounds group than in the positive-culture wounds group.

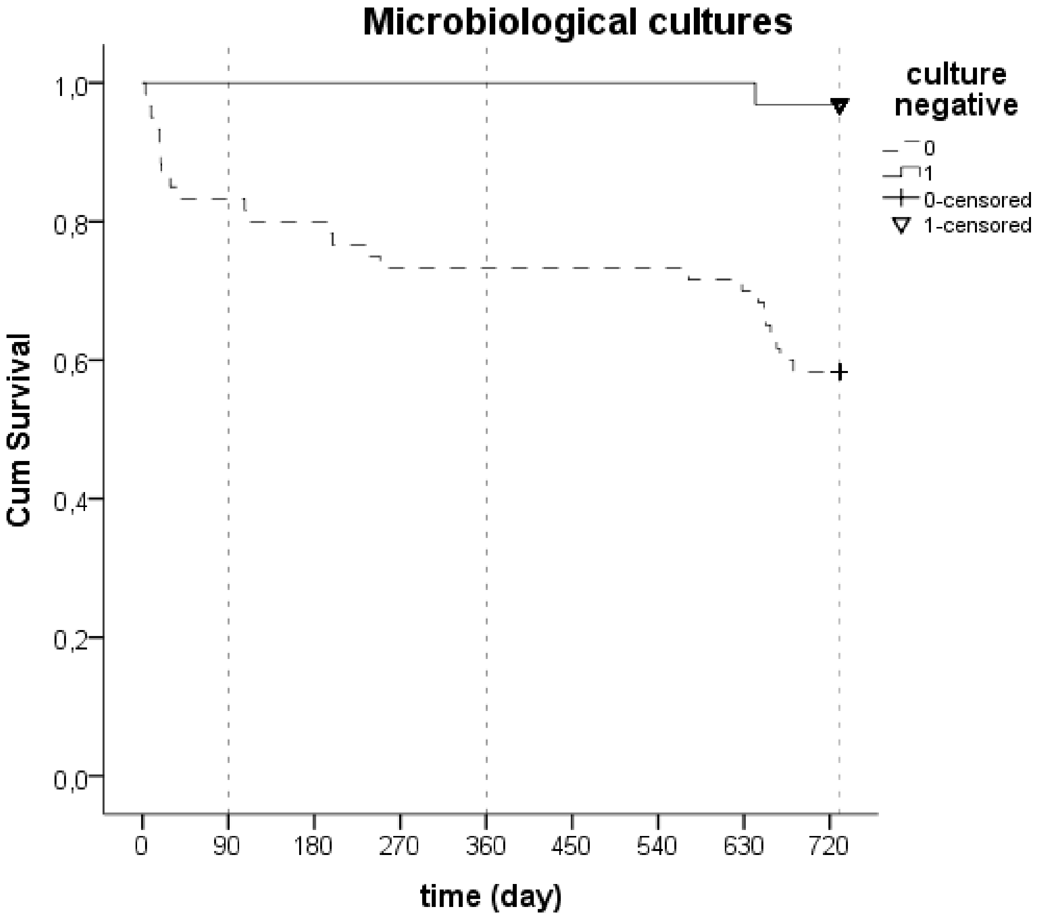


Figure 13. *The Kaplan–Meier estimates of survival rates for patients with culture negative and culture positive wounds, (Log rank tests; 90 days: p <0.001, 1 year p = 0,005, 2 years p = 0,003).*

6. DISCUSSION

6.1. Our retrospective observational study was the first study that attempted to assess the effect of INPWT on the wound-healing process after reconstructive surgery of DSWI. We observed a shorter Redon drainage time in the INPWT+Redons group. We assume that a decreasing amount of drainage is related, among many other factors, to the state of dead spaces in the area of reconstruction. The shorter period of Redon drainage might illustrate the extent of the obliteration of dead spaces after reconstruction, which might be the result of a vacuum effect exerted on the wound surface. The shorter hospital stay in the INPWT+ Redon group, compared to Redons only goup, indicated fewer complications regarding wound dehiscence and the development of seroma, which might be the result of the vacuum effect in reducing edema and improving the microcirculation conditions.

6.2. There are no broadly accepted guidelines for the treatment of DSWI or factors that would guide therapeutic decision-making. We attempted to clarify some factors that might contribute to the failure of surgical reconstruction. Knowledge of these factors would likely be useful to surgeons and help to decrease the rates of treatment failure and improve survival rates. In our study, we observed higher rates of treatment failure if infection appeared later during the wound healing process.
The role of positive wound culture at the time of reconstruction remains controversial.

In our study, we found that positive wound cultures contributed significantly to treatment failure.

We identified a significant contribution from peripheral vascular disease—poor microvasculature and low tissue hypoperfusion might underlie this observation. Other risk factors had no impact on surgical reconstruction failure.

Radical surgical debridement, even at the expense of sternectomy, and applying plastic surgical principles to wound treatment is more expedient than conventional surgical methods. A combination of radical surgical reconstruction with the applying of incisional negative pressure therapy has led to better surgical results, and shorter hospital stay in our patients.

6.3. We compared the treatment outcomes after conventional sternal rewiring and reconstruction without sternal rewiring in patients with DSWIs and detected higher readmission and early mortality rates in the sternal rewiring group.

Stable sternal osteosynthesis, appropriate tissue perfusion, and sterile environment are the three main elements necessary for uncompromised sternal wound healing. All of these factors must be kept in mind during sternal wound reconstruction. The surgical reconstruction of sternal wounds performed by cardiac surgeons is characterized by attempts to preserve the sternum and develop a biomechanically stable osteosynthesis. These procedures might involve a somewhat conservative sternal debridement and subsequent insertion of more wires into the infected wound. Where tissue perfusion is inadequate and in cases of poor microcirculation, (e.g., bilateral internal thoracic artery harvesting, obesity, diabetes mellitus, and peripheral vasculopathy), a stable osteosynthesis may not be sufficient for effective wound healing.

The role of foreign bodies, (i.e., wires and plates) in sternal wound infection recurrence has not been thoroughly examined. Elgharably et al. showed biofilms on sternal wires removed from the sternal wounds of six patients (47). Their findings might reflect the importance of eliminating all foreign bodies from infected wounds to obtain a sterile wound environment. Radical surgical debridement, even at the expense of partial or total sternectomy, followed by the application of plastic surgical techniques seems to be a more effective approach to sternal wound treatment than the use of conventional cardiac surgical methods. We prefer to prepare bilateral unpedicled rotational advancement flaps and unite them in an overlapping manner at the wound midline instead of using turnover flaps in patients who have undergone internal mammary artery harvesting.

Gram- positive bacterial cultures occurred more frequently in the sternal rewiring group than in the no sternal rewiring group. However, final sternal rewiring was only performed after microbiological cultures became negative.

6.4. Recently, there have been several efforts to reduce the prevalence of wound infections. Platelet-rich autologous plasma, gentamycin-coated sponge or vancomycin paste, or incisional negative pressure wound therapy are among those approaches that reportedly reduce the risk of wound infections. However, these measures do not target the surgical technique, which is a non-negligible risk factor, but are rather aimed at reducing microbiological contamination or promoting wound granulation. In our surgical experience, discharge from the sternal wounds appears, in most cases, at the lower part of these wounds. This observation led us to suspect the possible role of XIP in the development of these wounds. XIP is usually cartilaginous in adults. If XIP ossifies, the ossification process is usually more visible at the margins, with the core remaining cartilaginous. The healing process of cartilage tissue usually differs from that of bone. This is mainly because cartilage is avascular and the repair process after the damage to this tissue type is slow. Lachman et al. reported the existence of a xiphoid branch deriving from a trifurcation of the internal thoracic artery (48).

6.5. Negative microbiological results do not preclude the diagnosis of infection in the presence of definitive clinical signs, and according to the CDC criteria, diagnosis of wound infection might be established based on the intraoperative findings independently of the microbiological cultures. Many classifications of deep sternal wound infections (DSWI) were reported based on the time and localization of infection, risk factors, or intraoperative view. No available classification consider results of microbiological cultures an important concern. Negative-culture sternal wound infections are a common issue for the cardiac and plastic surgeon dealing with these wounds. Due to their impact on survival rates, classifying of clinical deep sternal wound infections on the base of microbiological culture would likely be useful.

7. NEW OBSERVATIONS

Our investigations on the role of microcirculation in the treatment and prevention of deep sternal wound infections resulted in new technical and clinical insights into the surgical management of primary and infected sternal wounds.

7.1. Although incisional negative pressure wound has been previously reported to be an effective procedure to reduce the risk of the deep sternal wound in high- risk patients, our work was the first to emphasize the impact of INPWT on infected sternal wounds reconstructed surgically. Our results show that accelerated obliteration of the dead spaces, early removal of Redon drains, and consequently higher success rates of surgical reconstruction might be achieved if INPWT is applied immediately after surgical reconstruction of sternal wounds.

7.2. Our work shows that, among those tested, peripheral vascular disease is the only risk factor that contributes to the development of sternal wound infections that might lead to failure of surgical treatment of these wounds. This finding demonstrates the significant impact of the microvasculature and tissue perfusion in preventing failure of surgical treatment. This might explain the better results obtained when well vascularized bilateral pectoral muscle flaps were used compared to simple sternal fixation. Improving the microcirculatory of these wounds might assist in the better transport of antibiotics to the site of infection.

7.3. Although sternal refixation might lead to a biomechanically stable thorax, our work shows that sternal rewiring is not mandatory in surgical reconstruction of these wounds, and that eliminating the infected sternum, even at the expense of hemi- or total sternectomy, and preservation of tissue perfusion by wound coverage by well- vascularized muscle flaps with a combination of INPWT, might also lead to stable thorax with complete freedom of symptoms.

7.4. Our work shows that the concept of the „XIP unit” is likely to be useful when dealing with deep sternal wounds. Xip- sparing midline sternotomy significanty (by almost 10- times) reduced the risk of DSWI after open heart surgery. We considered that dividing XIP in the middle would possibly result in poor cartilage healing and cartilage necrosis. This might be one of the initial steps that trigger infections of sternal wounds. We supposed that sparing the cartilaginous XIP with its muscle attachments, anteriorly to the linea alba and abdominal rectal muscle and posteriorly to the diaphragm, during midline sternotomy, in addition to preservation of the overlying skin and the bifurcation of the ITA, would assist in reducing the risk of sternal wound infections. The decrease in DSWI rates after XIP-sparing midline sternotomy underpins the importance of XIP unit preservation during midline sternotomy. In our patients, midline sternotomy with XIP unit preservation did not restrict access to any anatomical structure during surgery.

7.5. Our work has revealed that deep sternal wound infections are still a devastating complication after median sternotomy, even if standard microbiological cultures are negative. Failure of treatment occurs in ~20% of cases of negative culture wounds. However, in cases of successful surgical reconstruction, survival rates are better when wound cultures were negative. This might call for the significance of classifying sternal wound on the base of microbiological cultures, and reflect the fact that radical surgical debridement is mandatory, even if wound cultures are negative.

Considering the findings of our studies together, we sought to formulate an applicable treatment algorithm that would take into account all pillars of the sternal wound healing triad. The following algorithm is shown in Figure 15.

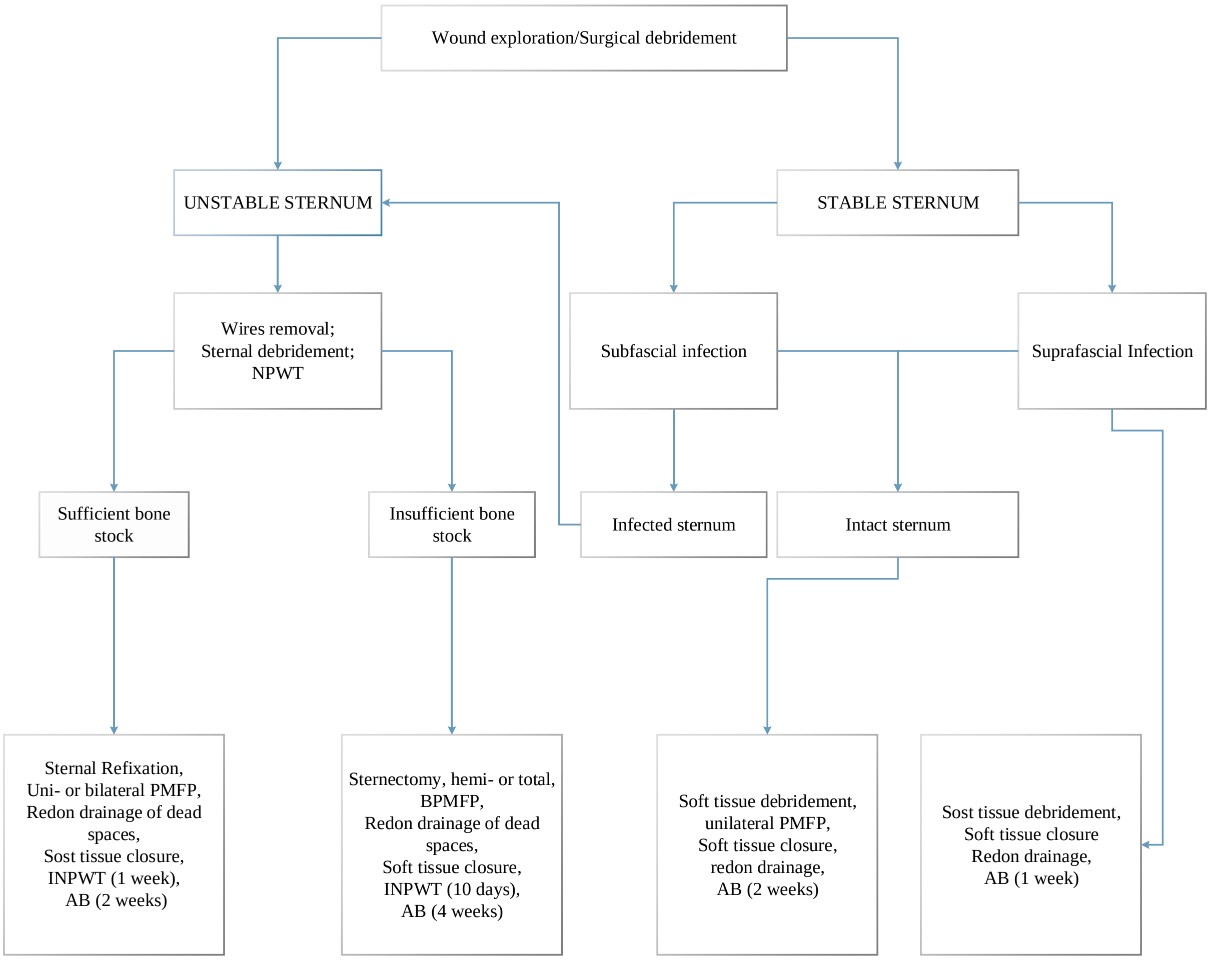


Figure 14. *Algorithm for the treatment of DSWIs.*

8. TOPIC-RELATED PUBLICATIONS

Aref Rashed, Magdolna Frenyó, Károly Gombocz, Sándor Szabados, Nasri Alotti. (2017) Incisional negative pressure wound therapy in reconstructive surgery of poststernotomy mediastinitis. INTERNATIONAL WOUND JOURNAL, 14 (1). pp. 180-183. ISSN 1742-4801. *IF: 2.848.*

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Rashed Aref és Frenyó, Magdolna és Fónagy, Gergely és Mazur, Mónika és Alotti, Nasri (2015) Incisionális negatív nyomás sebkezelés a poststernotomiás mediastinitis rekonstrukciós kezelésében. Cardiologia Hungarica, 45 (S J.). p. 1. ISSN 0133-5596

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Rashed Aref, Gombocz Károly, Frenyó Magdolna, Verzár Zsófia, Alotti Nasri. Sternotomiát követően létrejött sebfertőzések nyított és zárt kezelésével szerzett tapasztalaink pozitív sebváladék tenyésztési eredmények esetében. Magyar sebész Társaság, Kisérletes sebészeti szekció XXVI.kongresszusa, Herczeghalom, 2017. Szeptember 28-30.

Aref Rashed, Karoly Gombocz, Nasri Alotti, Zsofia Verzar (2017) Is sternal refixation a predictive factor for failure of treatment of deep sternal wound infections? In: 31st European Association of Cardiothoracic Surgery (EACTS), 2017.October 7-11, Vienna, Austria

Rashed Aref (2017): Az incisionális NPWT alkalmazása a szívsebészetben: In Elméleti Ismeretek és Gyakorlati Alkalmazás Negatív- Nyomás-Terápia. Budapest, pp.142-4. ISBN: 978-615-00-1000-7.

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Aref Rashed, Károly Gombocz, Nasri Alotti, Zsófia Verzár. Is Sternal Rewiring Mandatory in Surgical Treatment of Deep Sternal Wound Infections? J Thorac Dis 2018; 10(4): 2412-19. Doi: 10.21037/jtd.2018.03.166. *IF: 2.365.*

Rashed Aref, Frenyó Magdolna, Fónagy Gergely, Mazur Mónika, Alotti Nasri. Incizionális negatív nyomás terápia a poszt-szternotómiás mediastinitis reconstructiós kezelésében, Szeged, MSZT XXII. Kongresszusa, 2015.

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9. PUBLICATIONS UNRELATED TO THE TOPIC

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