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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ-από το Α ως το Ω»

Μεταπτυχιακή Διπλωματική Εργασία

" ΣΥΜΜΟΡΦΩΣΗ ΜΕ ΤΑ ΠΡΩΤΟΚΟΛΛΑ ΕΝΙΣΧΥΜΕΝΗΣ ΑΝΑΡΡΩΣΗΣ ΣΤΙΣ ΠΑΓΚΡΕΑΤΕΚΤΟΜΕΣ ΚΑΙ ΑΠΑΝΤΗΣΗ ΣΤΟ ΧΕΙΡΟΥΡΓΙΚΟ ΣΤΡΕΣ – ΜΙΑ ΜΗ ΠΑΡΕΜΒΑΤΙΚΗ ΠΡΟΟΠΤΙΚΗ ΜΕΛΕΤΗ ΠΑΡΑΤΗΡΗΣΗΣ "

υπό

ΓΕΩΡΓΙΟΥ ΖΑΧΑΡΟΠΟΥΛΟΥ

Ειδικευόμενου Χειρουργικής

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ-από το Α ως το Ω»

Λάρισα, 2025

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Τίτλος εργασίας στα αγγλικά:

Surgical stress response and compliance to ERAS protocols in pancreatic surgery – A non-interventional cohort prospective study

ΕΥΧΑΡΙΣΤΙΕΣ

Η ολοκλήρωση αυτής της μεταπτυχιακής διατριβής δεν θα ήταν δυνατή χωρίς την πολύτιμη βοήθεια, καθοδήγηση και στήριξη σημαντικών ανθρώπων, στους οποίους θα ήθελα να εκφράσω τις ειλικρινείς μου ευχαριστίες.

Αρχικά, θα ήθελα να ευχαριστήσω θερμά τον Καθηγητή μου και Μέντορα κ. Δημήτριο Ζαχαρούλη για την εμπιστοσύνη, την επιστημονική καθοδήγηση και την αμέριστη υποστήριξή του σε όλα τα στάδια της ιατρικής μου πορείας καθώς και της εργασίας αυτής. Η εμπειρία και η προσέγγισή του υπήρξαν καθοριστικές για την ολοκλήρωση της μελέτης.

Ευχαριστώ επίσης ιδιαίτερα τον Επίκουρο Καθηγητή κ. Δημήτριο Συμεωνίδη για τις πολύτιμες παρατηρήσεις του, την επιστημονική συμβολή του και τη διαρκή διαθεσιμότητά του.

Ιδιαίτερη μνεία θα ήθελα να κάνω στην Αναισθησιολόγο κα Δέσποινα Λιοτήρη για τη σημαντική της συμβολή, τη συνεργασία και την υποστήριξή της σε όλα τα στάδια της κλινικής εφαρμογής της μελέτης, χωρίς της οποία δεν θα μπορούσαν να τεθούν τα θεμέλια για αυτή την μελέτη.

Ακόμα θα ήθελα να ευχαριστήσω την Ειδικευόμενη Γυναικολογίας Αθηνά Σαμαρά, η οποία χάρη στις γνώσεις καθώς και την προθυμία της βοήθησε στην ορθή επεξεργασία και ερμηνεία των δεδομένων και την εκπόνηση της στατιστικής ανάλυσης.

Ευχαριστώ από καρδιάς την οικογένειά μου για την αδιάκοπη αγάπη, την κατανόηση και τη στήριξη που μου προσέφερε σε κάθε βήμα αυτής της διαδρομής. Η παρουσία τους αποτέλεσε σταθερό στήριγμα και πηγή δύναμης σε κάθε βήμα μου, ακόμα και αν αυτό έμοιαζε ασταθές.

Θα ήθελα επίσης να ευχαριστήσω τους φίλους μου και όλους όσοι στάθηκαν στο πλευρό μου με ενθάρρυνση, καλοσύνη και υπομονή, προσφέροντάς μου χαρά και ανακούφιση ακόμα και στις πιο απαιτητικές στιγμές.

Σε όλους όσους, με τον δικό τους τρόπο, συνέβαλαν στην πραγματοποίηση αυτής της προσπάθειας, εκφράζω την ειλικρινή μου ευγνωμοσύνη.

Περίληψη

Εισαγωγή

Τα πρωτόκολλα ταχείας ανάρρωσης μετά από χειρουργείο (ERAS) στοχεύουν στη μείωση του χειρουργικού στρες και στη βελτίωση των μετεγχειρητικών αποτελεσμάτων. Σκοπός της μελέτης μας είναι να αξιολογηθεί κατά πόσο η χειρουργική καταπόνηση, όπως μετράται μέσω του λόγου ουδετερόφιλων προς λεμφοκύτταρα (NLR) και του λόγου αιμοπεταλίων προς λεμφοκύτταρα (PLR), σχετίζεται με το επίπεδο συμμόρφωσης στο πρωτόκολλο και τα αποτελέσματα των ασθενών που υποβάλλονται σε ανοικτή παγκρεατοδωδεκαδακτυλεκτομή (PD).

Μεθοδολογία

Πρόκειται για προοπτική μη-επεμβατική μελέτη σειράς, η οποία πραγματοποιήθηκε σε ένα εξειδικευμένα κέντρο αναφοράς για τον καρκίνο του παγκρέατος στην Κεντρική Ελλάδα. Όλοι οι συμμετέχοντες ασθενείς ακολούθησαν ένα τυποποιημένο πρωτόκολλο ERAS για την παγκρεατική χειρουργική. Συλλέχθηκαν προοπτικά δεδομένα για τους δείκτες NLR, PLR, το ποσοστό συμμόρφωσης στο πρωτόκολλο και τα μετεγχειρητικά αποτελέσματα.

Αποτελέσματα

Βρέθηκε συσχέτιση μεταξύ της συμμόρφωσης στο πρωτόκολλο και της χειρουργικής καταπόνησης. Συγκεκριμένα, υψηλότερα ποσοστά συμμόρφωσης σχετίζονταν με στατιστικά σημαντικές χαμηλότερες τιμές PLR την τέταρτη μετεγχειρητική ημέρα (Spearman’s rho -0.301, p=0.004). Επίσης, υψηλότερες προεγχειρητικές τιμές PLR αντιστοιχούσαν σε χαμηλότερα ποσοστά συμμόρφωσης (Spearman’s rho -0.276, p=0.008). Την πρώτη μετεγχειρητική ημέρα, χαμηλότερες τιμές NLR (p=0.007) και PLR (p=0.018) σχετίζονταν με αυξημένη πιθανότητα εμφάνισης επιπλοκών.

Συμπεράσματα

Η παρούσα προοπτική μελέτη αξιολογεί τη σχέση μεταξύ χειρουργικής καταπόνησης, συμμόρφωσης με το ERAS και των μετεγχειρητικών εκβάσεων στην παγκρεατική χειρουργική. Τα ευρήματα δείχνουν ότι η υψηλότερη συμμόρφωση στο ERAS μειώνει τη χειρουργική καταπόνηση, ιδίως έως την τέταρτη μετεγχειρητική ημέρα. Οι αυξημένες προεγχειρητικές τιμές PLR ενδέχεται να προβλέψουν τη συμμόρφωση στο πρωτόκολλο, ενώ οι τιμές των NLR και PLR μετά την επέμβαση

μπορούν να υποδείξουν την πιθανότητα επιπλοκών. Αυτοί οι εύκολα προσβάσιμοι δείκτες μπορούν να συμβάλλουν στην πρόβλεψη της επιτυχίας εφαρμογής του ERAS στην παγκρεατική χειρουργική.

Λέξεις- Κλειδιά: ERAS, NLR, PLR, παγκρεατοδωδεκαδακτυλεκτομή, PD, χειρουργική καταπόνηση,

Abstract

Introduction

Enhanced recovery after surgery (ERAS) protocols aim to attenuate surgical stress and improve postoperative outcomes. Our purpose is to assess whether the surgical stress response, measured through the neutrophil-to-lymphocyte ratio (NLR) and the platelets-to-lymphocyte ratio (PLR) is associated with the level of compliance to the protocol and outcomes of patients undergoing open pancreatoduodenectomy (PD).

Methodology

This prospective non interventional cohort study is conducted at a high-volume referral center for pancreatic cancer in Central Greece. All recruited patients follow a standardised ERAS pathway for pancreatic surgery. We collected prospective data on NLR and PLR preoperatively and on the first five postoperative days, as well as the compliance rate with the protocol and patient outcomes.

Results

A correlation was found between compliance and surgical stress response. Specifically, higher compliance rates are associated with lower PLR on the fourth postoperative day (Spearman's rho -0.301, p=0.004). Furthermore, higher preoperative PLR levels correspond to lower compliance rates (Spearman's rho -0.276, p=0.008). On the first postoperative day, lower NLR (p=0.007) and PLR (p=0.018) values are associated with increased potential for complications

Conclusions

This prospective study assesses the relationship between surgical stress response, ERAS compliance, and outcomes in pancreatic surgery. Findings indicate that higher adherence to ERAS protocol is associated with reduced surgical stress, particularly by the fourth postoperative day. Elevated preoperative PLR may predict protocol adherence, while postoperative NLR and PLR could indicate patient outcomes. These readily available metrics may help predict ERAS success in reducing surgical stress in pancreatic surgery.

Key words: ERAS, NLR, PLR, pancreatoduodenectomy, PD, surgical stress,

Πίνακας Περιεχομένων

General part

Chapter 1 Introduction

1.1 Pancreatic cancer and surgical stress

Pancreatic cancer is the 12th most prevalent cancer globally; however, it ranks as the 6th leading cause of cancer-related mortality.[1] Both its incidence and mortality have been rising over the years. [2] The median age of diagnosis is 70 years, and the incidence is comparable across genders, with a slight predominance observed in males. Approximately 60-70 % of pancreatic exocrine tumors are located in the head of the pancreas, while 20-25 % are found in the body and tail. The remaining tumors are characterized by diffuse involvement across the pancreas. [3]

Pancreatoduodenectomy, commonly referred to as the "Whipple procedure", is the preferred surgical treatment for tumors located in the pancreatic head and uncinate process. [4] However, this complex procedure carries a high percentage of complications, such as pancreatic fistula, delayed gastric emptying, postoperative bleeding, bile leakage, and liver failure, to name a few. [5-10] These complications result in prolonged hospital stay and mortality. The complexity of this procedure stems from the need to resect and reconstruct many different structures, including the pancreas, duodenum, bile duct, and stomach. Pancreatic anastomosis is particularly susceptible to leaks due to the delicate pancreatic tissue and the enzymatic activity that can cause further tissue damage.[11]

In 1997, Prof. Henrik Kehlet identified various factors contributing to postoperative morbidity, including pain, infections, and complications associated with the cardiovascular, pulmonary, and gastrointestinal systems. The underlying commonality among these factors is the surgical stress response experienced by the patient.[12]

The surgical stress response refers to a series of physiological changes in homeostasis, encompassing alterations in hormonal, metabolic, inflammatory, and other processes within the organism, which occur in response to trauma.[13] The increased production of cortisol, catecholamines, and glucagon, along with simultaneous insulin resistance, leads to heightened catabolic activity. Cellular injury results in the release of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF), which not only activate the inflammatory response but also disrupt homeostasis. This disruption affects both the sympathetic nervous system and the secretion of hormones.

[13] All of the aforementioned factors contribute to the functional impairment of various organs, resulting in a range of complications. Moreover, an excessive stress response may lead to immunosuppression, thereby increasing the vulnerability of patients to infections, delayed wound healing, and sepsis. [11] Given the significant complexity of the Whipple procedure and its associated morbidity rate, which approaches 55% [14], surgical stress emerges as a critical factor influencing patient outcomes.[15]

Kehlet's research has highlighted the significance of multimodal perioperative care, emphasizing the various stressors involved and strategies for their mitigation. His contributions have thus established the foundational principles for the implementation of Enhanced Recovery After Surgery protocols [15].

1.2 ERAS Protocols in Pancreatic Surgery

The Enhanced Recovery After Surgery (ERAS) protocols for pancreatic surgery were first established in 2012, providing a framework for standardized, evidence-based perioperative care pathways. In 2018, Hai-Bi Jin and colleagues demonstrated the safety and efficacy of these ERAS protocols, reporting a reduction in complication rates and an improvement in the postoperative recovery of patients [16]. In accordance with the initial protocols established in 2012, the ERAS Society introduced updated guidelines in 2019. These guidelines aim to refine perioperative strategies that facilitate expedited recovery and reduce the incidence of complications. [15]

The guidelines are divided into three main phases: preoperative, intraoperative, and postoperative.

Preoperatively, the implementation of prehabilitation is essential. This includes encouraging patients to initiate physical activity, optimize their dietary practices, and cease the consumption of alcohol and tobacco products, all of which can significantly impact the postoperative recovery period [16]. Furthermore, administering carbohydrate loading before surgery, in the absence of bowel preparation, has been demonstrated to reduce insulin resistance and mitigate catabolic stress. [17]

In the perioperative phase, the preference for regional anesthesia techniques and multimodal anesthesia, as opposed to the reliance on opioids, can significantly mitigate complications associated with opioid use [18],[19] . The implementation of a goal-directed fluid therapy algorithm serves to prevent fluid overload and its associated

complications [20]. Additionally, it is imperative to reduce nausea and vomiting through appropriate therapeutic interventions, while facilitating the early removal of the nasogastric tube to promote expeditious bowel recovery [21].

In the postoperative phase, early oral intake and patient mobilization are essential to prevent complications such as delayed gastrointestinal function and deep venous thrombosis. Moreover, timely removal of drains is important to reduce infection risk [22]

Following the adoption of ERAS protocols, continuous studies have enhanced the previously mentioned techniques, with a particular emphasis on adherence [23]. The higher the adherence to ERAS guidelines the better the patient outcomes, including fewer days of hospital stay, fewer complications, and lower healthcare costs [24]. Although strong evidence supports the importance of ERAS, compliance varies due to factors such as patient and surgeon preferences, as well as institutional contexts. [25] Evaluating the degree of adherence to these protocols in pancreatic surgery remains a critical area of research, highlighting the need for ongoing education and protocol standardization in favor of the patient.

1.3 Surgical stress response and ERAS

Research has thoroughly examined how surgical stress affects recovery after surgery, emphasizing its role in complications and extended healing time. In a recent review, Ivascu R et al. highlight that excessive surgical stress causes metabolic and immune disruptions, resulting in increased catabolism and immunosuppression, which are particularly critical in high-risk surgeries such as pancreaticoduodenectomy. Increased levels of IL-6 and TNF-α have been associated with a higher incidence of pancreatic fistula formation and infections, highlighting the necessity for effective stress modulation during perioperative care.[26] A study published in BMC Surgery in 2024 examined various anesthetic techniques aimed at reducing surgical stress during pancreatic procedures.[27] The results showed that total intravenous anesthesia (TIVA) with propofol provides immunomodulatory benefits by reducing inflammatory markers and speeding up recovery, compared to inhalational anesthesia. These findings support the ERAS principles, which promote multimodal approaches to minimize physiological stress.[28]

Since their introduction in 2012, ERAS protocols for pancreatic surgery have been widely studied for their effectiveness. Multiple systematic reviews and meta-analyses confirm that ERAS implementation significantly decreases postoperative complications, accelerates recovery, and shortens hospital stay without increasing readmission rates.[29] Additionally, a recent meta-analysis supports the safety of ERAS, showing a 20-30% reduction in overall morbidity.[15][16][30][31]

A key study by Hai-Bi Jin et al. (2018) showed that ERAS protocols decrease the incidence of delayed gastric emptying and postoperative ileus, two common complications following the Whipple procedure.[16] Additionally, a 2020 randomized controlled trial highlighted the importance of early oral nutrition and mobilization - key elements of ERAS - in reducing infection rates and improving gastrointestinal function.[32]

Despite the strong evidence supporting ERAS protocols, adherence to these guidelines varies among institutions. A study by Morgan KA et al. in 2015 found significant compliance differences, with lower adherence associated with higher complication rates.[32] Recent research is exploring the link between ERAS compliance and patient outcomes, as studied by Liotiri D et al.[33]

A burgeoning area of research focuses on utilizing biomarkers to evaluate surgical stress and the effectiveness of ERAS protocols. Investigations into the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) suggest that these markers could serve as objective indicators of the body's stress response and recovery process.[34] Integrating biomarker analysis into the monitoring of ERAS compliance may improve adherence and optimize patient outcomes.

G Spolverato et al. in their study concluded that among the factors associated with shorter relapse-free survival (RFS) after hepato-pancreatico-biliary resections was the elevated preoperative PLR value [35]. Specifically, a preoperative PLR value over 190 was associated with the occurrence of postoperative complications and worse overall survival. In another study Giakoustidis A. et al. considered as elevated values for NLR and PLR 4 and 120 respectively. Patients who had normal values of PLR and NLR preoperatively had better overall survival (OS) than patients with elevated NLR or PLR and patients with both NLR and PLR elevated had the worst OS.[36] Maloney S. et al.

also suggest that higher NLR values are related with shorter OS. Especially NLR>5 postoperatively, is associated with short OS in patients either with neoadjuvant therapy or with upfront surgery.[37] In a study comparing patients with resected colorectal cancer, the group following the ERAS protocol had significantly lower postoperative NLR and fewer complications than those who did not follow the protocol.[38]

Specific part

Chapter 2 Methodology

2.1 Aim

Our study aims to evaluate the impact of compliance with the ERAS protocol on the stress response following open pancreaticoduodenectomy (PD) for pancreatic cancer.

The primary objective is to assess how compliance with this protocol affects the surgical stress response, measured through the NLR and the PLR. These ratios will be assessed both preoperatively (from one week to one day before the operation) and postoperatively (during the first five days following the procedure).

The secondary outcome is to explore how variations in NLR and PLR affect postoperative outcomes, providing valuable insights for improving patient care and recovery processes.

2.2 Inclusion/exclusion criteria

Inclusion criteria: participants must be over 18 years old, engaged in the enhanced recovery protocol, undergoing elective open pancreaticoduodenectomy (PD) for pancreatic cancer, fluent in Greek, and without communication barriers.

Exclusion criteria: Age under 18, inability or unwillingness to participate in the enhanced recovery protocol, undergoing other pancreatic surgeries (including peripheral and total pancreatectomies, laparoscopic procedures, emergency cases, or palliative pancreaticoduodenectomies), missing data, or loss to follow-up.

2.3 Study design

Ethics approval

The study protocol has been approved by the ethics committee of the Faculty of Medicine of University of Thessaly. Approval has also been granted by IASO Hospital Institutional Review Board and by Scientific Board of University Hospital of Larissa.

Study design

This is a prospective observational cohort study. STROBE reporting guidelines are followed [39]. Additionally, we utilize the RECOvER Checklist, which is designed to provide a standardized framework for reporting ERAS-related studies [40].

Study setting

The study has taken place in IASO Hospital (largest private general hospital in Thessaly), with stable group of surgeons and anesthesiologists. All patients undergoing elective open PD between June 2022 and January 2025 have been recruited.

Patients have been enrolled in the study prospectively after providing written informed consent. These enrolled patients have followed the ERAS pathway specifically designed for pancreatic surgery throughout the preoperative, intraoperative, and postoperative periods. The ERAS protocol is based on recommendations from the ERAS Society for enhanced recovery after pancreatoduodenectomy. The study group utilized a checklist of ERAS criteria [Figure 1] to monitor each patient, and data were collected on adherence rates to these criteria. An electronic database, specifically a protected Excel spreadsheet, was employed for prospective data collection.

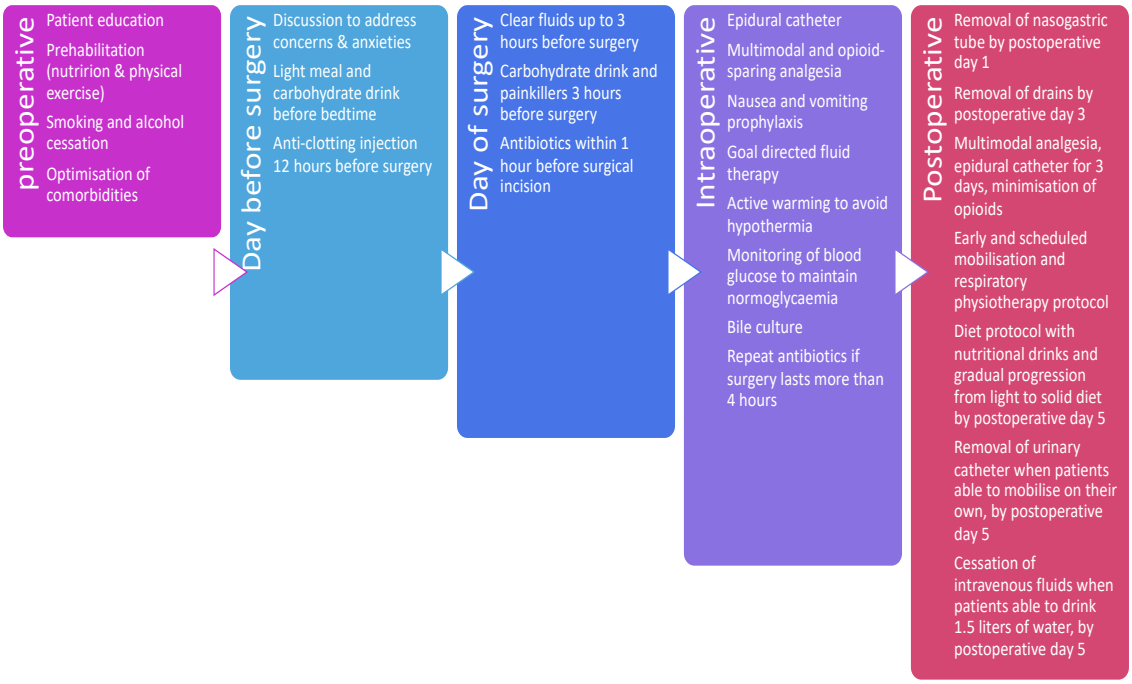

Figure 1 Local ERAS protocol for pancreatic surgery

Data were collected on patient demographics, including sex, age, and body mass index (BMI), as well as the American Society of Anesthesiologists (ASA) physical status, co-morbidities, surgical approach, technique, and pTNM stage.

Information on complications was also gathered, encompassing cardiovascular and respiratory complications, infectious complications (such as surgical site infections, chest infections, urinary tract infections, intra-abdominal abscesses, and sepsis), anesthetic complications (including severe pain, delirium, and cognitive decline), functional complications (like functional decline, new mobility aid use, pressure ulcers, and discharge to nursing or rehabilitation facilities), renal failure, ileus, return to the operating room, readmission, and mortality.

Furthermore, data were collected on the length of hospital stay and pancreatic surgery-specific complications, including delayed gastric emptying (DGE), post-pancreatectomy hemorrhage (PPH), and postoperative pancreatic fistula (POPF) formation.

After anonymization, all data were prospectively uploaded by local investigators to a secured database and included in a spreadsheet for analysis.

2.4 Definitions

Postoperative complications were defined as any complication within 30 days from surgery, and their severity was graded according to the Clavien-Dindo classification system [41]. Complications were divided into minor (Grades I and II) and major complications (Grades III and IV).

DGE was defined according to the International Study Group of Pancreatic Surgery (ISGPS) as the requirement or re-insertion of NGT after the third postoperative day or inability to tolerate oral diet by the seventh postoperative day [9]. There are three grades of DGE (A, B, C) as defined by ISGPS according to severity.

POPF was defined according to the International Study Group for Pancreatic Fistula (ISGPF) as drain output of any measurable volume on or after the third postoperative day with amylase content greater than three times the upper normal serum value [6]. There are three grades of POPF (A, B, C) as defined by ISGPF based on severity.

PPH was also defined, according to the ISGPS guidelines, as early (<24 hours) or late (>24 hours) intraluminal or extraluminal, and mild, moderate, or severe hemorrhage post-PD [10]. There are three grades of PPH according to severity and clinical impact.

The length of hospital stay referred to the time from the date of surgery to the date of discharge.

Readmission was defined as a readmission within 30 days of discharge.

2.5 Statistical analysis

Statistical analysis was carried out using R statistical environment software (R Core Team (2024). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/) and JASP (University of Netherlands).

The data were analyzed using NLR and PLR ratios, postoperative complications, and length of hospital stay as the main outcome variables.

The influence of the following factors was assessed: age, BMI, sex, ASA classification, and compliance with the ERAS protocol. Adherence was calculated as the number of interventions fulfilled/20 (total number of preoperative and perioperative interventions).

Univariate analysis was undertaken to assess the relationship between each factor and the outcome variables. Multivariate regression analysis was then performed for all variables in the univariate analysis with a P value < 0.05. Sample size guidelines for observational studies with regression analysis are based on simulation studies and suggest that the minimum number of events per variable (EPV) should be 10. [17,18] According to these guidelines the minimum sample size is calculated at 90.

All patient data were anonymized and transferred onto a Microsoft Excel spreadsheet for descriptive analysis. We carried out a statistical analysis using the R statistical environment software [42]. We compared continuous variables with One-Way ANOVA or Student's t test for parametric data and with a non-parametric test (Mann-Whitney U test or Kruskal-Wallis test), as indicated. For analysis of categorical data, we used the chi squared or Fisher's exact test where indicated. Quantitative values were expressed as mean ± standard deviation (SD), median and range, categorical data with percentage frequencies. Differences in complications between different degrees of compliance were assessed by the application of log rank test. P value< 0.05 was considered as statistically significant. The odds ratio (OR) presented followed by 95% confidence interval (95% CI). Differences in complications between different degrees of compliance were assessed by the application of log rank test. P < 0.05 was considered statistically significant.

Chapter 3 Results

Results

3.1 Patient characteristics

Based on study criteria, 92 consecutive patients that underwent an elective pancreatoduodenectomy for pancreatic cancer under the ERAS protocol were included in the study (Figure 2). The mean age was calculated at 67.2 (11.5) years and 52 (56.5%) of them were male patients. The mean BMI was 25.9 and all patients had an ASA score II or III. Moreover, the average compliance rate was calculated at 72.7% (15.5).

3.2 Synthesis of outcomes

The mean and standard deviations (SD) values of NLR and PLR from the preoperative day to the 5th postoperative day are displayed on Table S1.

The incidence of any complication was estimated at 32%, while the risk for severe complications (Clavien-Dindo more than II) was 8.7% respectively.

3.2.1 NLR and ERAS compliance

When correlated ERAS compliance rate with NLR values, a positive correlation was observed between NLR values and ERAS compliance rate (Table 1). However, this positive correlation (r=0.244) was statistically significant only on the first postoperative day (p=0.019). Moreover, ERAS compliance rate and ΔNLR values were statistically significant (p=0.043) positively correlated (0.211), meaning that greater difference between maximum postoperative and preoperative NLR values is correlated with greater ERAS compliance rate (Figure 3).

3.2.2 PLR and ERAS compliance

Regarding the correlation between ERAS compliance rate and PLR, a statistically significant (p=0.008) negative correlation (r=-0.276) was observed between preoperative values and ERAS compliance (Table 1). In a similar way, a statistically significant (p=0.004) negative correlation (r=-0.301) between PLR measured on the fourth postoperative day and ERAS compliance was noted. On the other hand, a statistically significant positive correlation (r=0.246) was observed on the first postoperative day (p=0.018). (Figure 4) depicts the statistically significant correlations between PLR and ERAS compliance rate.

3.2.3 NLR and severe complications

On Table 3 are displayed the mean values of NLR grouped by patients diagnosed with a severe complication during the first 30 days postoperatively and those without. When comparing the mean NLR values on the first postoperative day, a statistically significant lower mean NLR value was observed in the patients that experienced a severe postoperative complication (p=0.007). In a similar manner, the mean difference between maximum postoperative and preoperative values of NLR (ΔNLR) was

statistically significant lower in the group of patients with a severe postoperative complication (p=0.02).

3.2.4 PLR and severe complications

The mean values of PLR grouped by the presence of a severe complication are reported in Table 3. Similar to NLR values, when comparing the mean PLR values, both PLR on the first postoperative day and ΔPLR in patients complicated by a severe postoperative complication, were statistically significant lower (p=0.009 and p=0.005 respectively).

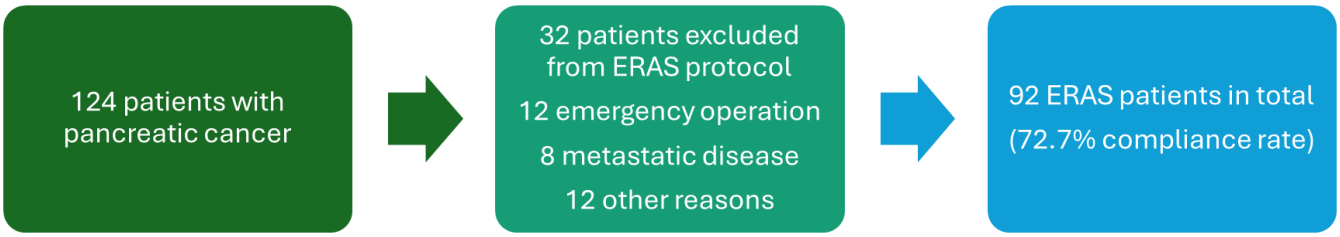

Figure 2 Flow chart

Variable		NLR PREOP	NLR POD1	NLR POD2	NLR POD3	NLR POD4	NLR POD5	ΔNLR
ERAS COMPLIANCE (%)	Spearman's rho	0.024	0.244	0.125	0.103	0.072	0.164	0.211
	p-value	0.820	**0.019**	0.234	0.329	0.493	0.119	**0.043**

Table 1 Correlations between NLR values and ERAS compliance rate.

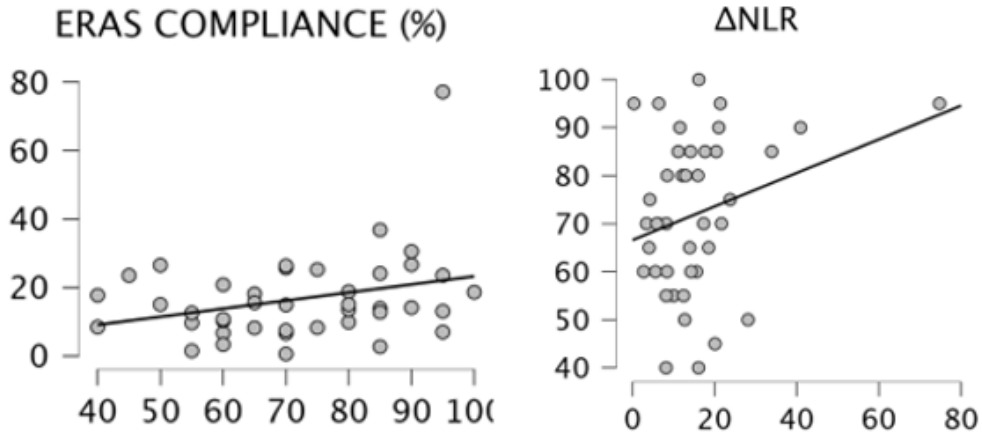

Figure 3 A and B: Correlation between A: NLR values on the first postoperative day and ERAS compliance rate (r=0.244, p=0.019) B: ΔNLR values and ERAS compliance rate (r=0.211, p=0.043).

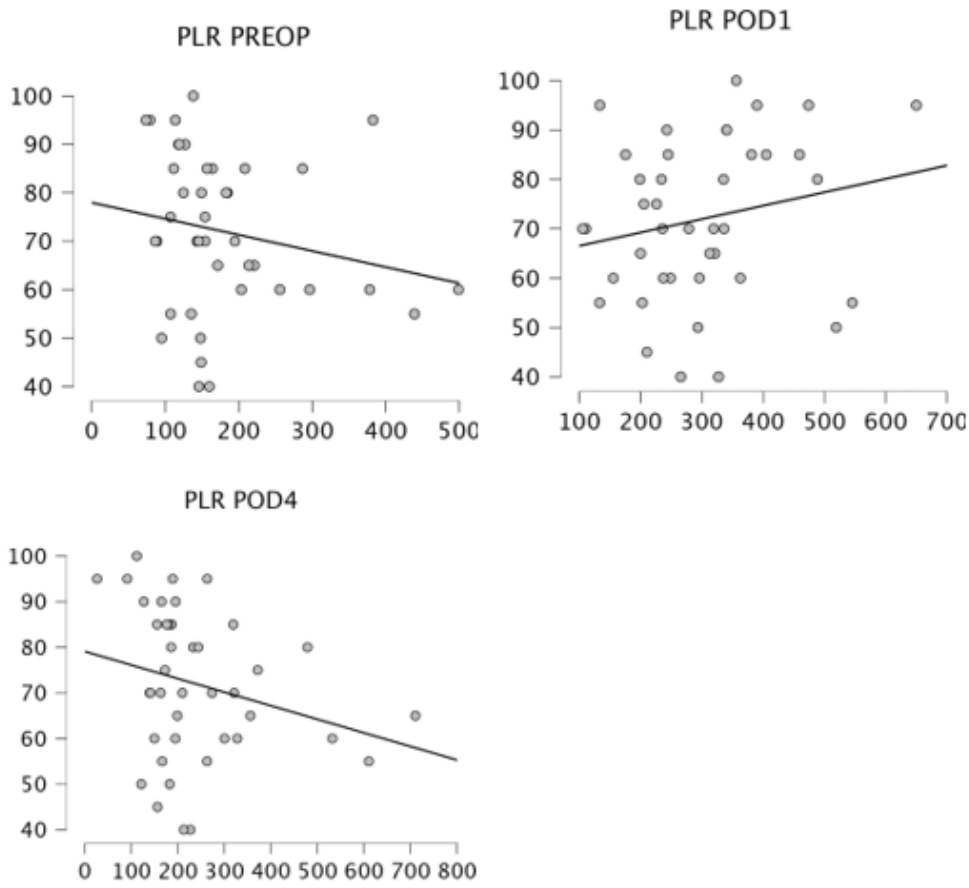

Figure 4 A, B and C: Correlation between A: PLR preoperative values and ERAS compliance rate (r=-0.276, p=0.008), B: PLR values on the first postoperative day and ERAS compliance rate (r=0.246, p=0.018) and C: PLR values on the fourth postoperative day and ERAS compliance rate (r=-0.301, p=0.004).

Variable		**PLR PREOP**	**PLR POD1**	**PLR POD2**	**PLR POD3**	**PLR POD4**	**PLR POD5**	**ΔPLR**
ERAS COMPLIANCE (%)	Spearman's rho	-0.276	0.246	0.015	-0.070	-0.301	-0.174	0.169
	p-value	**0.008**	**0.018**	0.888	0.507	**0.004**	0.105	0.107

Table 2: Correlations between PLR values and ERAS compliance rate.

	Severe complication	**N**	**Mean**	**SD**	**SE**	**p-value***
NLR PREOP	No	84	3.686	3.288	0.359	0.144
	Yes	8	2.394	1.256	0.444	
NLR POD1	No	84	17.248	12.344	1.347	**0.007**
	Yes	8	7.342	5.370	1.899	
NLR POD2	No	84	13.379	7.960	0.868	0.210
	Yes	8	9.302	3.991	1.411	
NLR POD3	No	84	11.466	5.771	0.630	0.095
	Yes	8	7.233	2.998	1.060	
NLR POD4	No	84	8.235	4.255	0.464	0.734
	Yes	8	7.064	3.088	1.092	
NLR POD5	No	84	6.931	3.526	0.385	0.228
	Yes	8	5.610	2.542	0.899	
ΔNLR	No	84	15.877	12.287	1.341	**0.020**
	Yes	8	8.302	3.722	1.316	
PLR PREOP	No	84	171.524	81.623	8.906	0.060
	Yes	8	255.339	152.950	54.076	
PLR POD1	No	84	307.839	120.976	13.200	**0.009**
	Yes	8	204.812	48.175	17.033	
PLR POD2	No	84	225.448	113.073	12.337	0.841
	Yes	8	205.082	57.917	20.477	
PLR POD3	No	84	220.178	110.970	12.108	0.442
	Yes	8	181.578	68.207	24.115	

PLR POD4	No	84	242.727	140.009	15.276	0.510
	Yes	8	207.069	75.634	26.741	
PLR POD5	No	80	257.276	147.053	16.441	0.357
	Yes	8	217.480	114.459	40.468	
ΔPLR	No	84	197.473	126.441	13.796	**0.005**
	Yes	8	16.460	178.025	62.941	

Table 3: NLR and PLR mean values regarding severe complication.

*Mann-Whitney test

Variable	**PLR PREOP**	**PLR POD1**	**PLR POD2**	**PLR POD3**	**PLR POD4**	**NLR PREOP**	**NLR POD1**	**NLR POD2**	**NLR POD3**	**NLR POD4**	**NLR POD5**
Mean (SD)	179 (92.3)	298.79 (120.6)	223.58 (109.9)	216.73 (108.8)	239.53 (136.5)	3.48 (3.2)	16.29 (12.1)	12.93 (7.8)	11.01 (5.8)	8.04 (4.2)	6.79 (3.5)

Supplementary table S1: Mean values of PLR and NLR.

Chapter 4 Discussion

Overview of findings

In this study, we investigated the correlation between ERAS protocols and the postoperative inflammatory markers PLR and NLR in patients who had a pancreatoduodenectomy procedure for pancreatic cancer. Furthermore, we investigated the correlation between these markers and postoperative complications.

There was a positive correlation between ERAS compliance and NLR on the first postoperative day and ΔNLR. On the other hand, a negative correlation was observed between PLR and ERAS compliance preoperatively and on postoperative day 4; however, the correlation on the first postoperative day was positive. Finally, patients who had lower NLR and PLR values on the first postoperative day developed severe complications. Additionally, severe complications were observed in patients with significantly lower ΔNLR and ΔPLR compared to those without complications.

Interpretation in the context of other evidence

The correlation between ERAS protocols compliance and the postoperative inflammatory markers, especially NLR and PLR, shows an intricate balance between the surgical stress that occurs, the different immune system activation, and the recovery rate.

The aim of ERAS protocols, as mentioned before, is to reduce surgical stress and optimize immune and metabolic function, thereby facilitating faster recovery. To our surprise, our study reveals that the higher the ERAS compliance, the higher the NLR and PLR were found on postoperative day (POD) 1, with a greater ΔNLR. Several studies have demonstrated that early enteral feeding, a key component of ERAS protocols, facilitates early gastrointestinal tract mobility and immune reactivation, as indicated by elevated leukocyte counts [43].

In contrast to them, patients with lower NLR and PLR were more prone to develop severe complications. This effect can be explained by the Compensatory Anti-inflammatory Response Syndrome (CARS) following Systemic inflammatory Response Syndrome (SIRS), where homeostasis is tried to be restored leading to immunosuppression. As a result, patients can't respond to challenges such as infections and anastomotic leaks [44]. Normally, these two procedures are following

one another, so the organism can heal the initial injury without causing secondary injuries.

We found a negative correlation between preoperative PLR and compliance with the ERAS protocol. An elevated preoperative PLR, as noted earlier, is linked to an increased risk of postoperative complications and poorer overall survival. Given this information, we can better anticipate outcomes in the immediate postoperative period as well as the long-term results.

Moreover, a negative correlation was observed between ERAS compliance and the PLR value on postoperative day 4 (POD 4). This suggests that non-compliant patients may experience a prolonged inflammatory phase that does not resolve by POD 4, potentially leading to more complications and a delayed recovery. It is essential to note that we should monitor our patients before, during, and after surgery using a series of markers, rather than relying solely on a single marker.

Implications for practice

Our study supports that the use of NLR and PLR markers, in addition to being cost-effective and easily available, can help the clinical doctor distinguish the patients who are at higher risk to develop severe complications. In this setting, having these markers in the ERAS quiver in the preoperative and the postoperative phase, early identification of patients who need closer monitoring can help to prevent the appearance of clinical signs, to avoid major complications, and support them accordingly. Low NLR or PLR values during POD 1 or a persistent elevation of PLR on POD 4 can define which patients may need early imaging or intervention.

Furthermore, a well-tempered sequencing between the initial inflammatory response and the return to homeostasis without exacerbated stress is the final target. In this way, we are not only limited to achieving a faster recovery and less morbidity, but we also enhance the organism to achieve a more natural and normal recovery.

Taking into account the values of NLR and PLR of POD 1, the PLR of POD 4, and the patient's condition, we can determine the appropriate time for the patient's discharge, making a more personalized and evidence-based decision.

Implications for future research

Larger prospective studies are essential to confirm the correlations between ERAS and these biomarkers, as well as to establish specific threshold values that could serve as early indicators for patients who are at risk of developing major complications. Moreover, a correlation between specific ERAS components and their effect on the inflammatory response and specific complications would be enlightening.

Finally, a complex of inflammatory markers, other biochemical values (from serum or drainage), or clinical signs could help develop a predictive model for risk stratification after pancreatic surgeries. Having such a tool can facilitate the real-time determination of risk for postoperative complications.

Limitations

To the best of our knowledge, our study is one of the first that studied the impact of ERAS protocol in surgical stress response in patients that underwent pancreatoduodenectomy for cancer. Our data have a low level of heterogeneity, being a single-center, prospective cohort study, meaning that other institutions, employing different techniques, patient populations, and Enhanced Recovery After Surgery (ERAS) implementations, could contribute valuable insights to our results.

. Moreover, the relevant low rate of missing data, the prospective design and the high compliance rate are major strengths of our study.

However, several limitations must be considered in our study. We included 92 patients, of whom only 8 experienced severe complications, resulting in low statistical power, particularly in the subgroup analyses. Larger studies are needed to validate our findings.

Moreover, the impact of each individual component of ERAS compliance was not assessed. Consequently, we cannot determine which specific aspects had the greatest effect on postoperative inflammatory changes. One of the future directions of our study is to recruit a larger patients' cohort and investigate the exact impact of each component of the ERAS protocol on surgical stress response.

Furthermore, incorporating additional biomarkers such as C-reactive protein (CRP), albumin, or procalcitonin—each of which is widely available—could help explain the inflammatory profile of each patient.

Chapter 5 Conclusions

This prospective observational study demonstrated that adherence to the Enhanced Recovery After Surgery (ERAS) protocol in pancreatic surgery is associated with regulation of the postoperative inflammatory response. Specifically, higher ERAS compliance correlated with a decrease in NLR and PLR, which are simple, cost-effective biomarkers reflecting surgical stress response.

Importantly, patients who developed severe complications exhibited significantly lower postoperative NLR and PLR values, suggesting that an insufficient or suppressed immune response may be predictive of adverse outcomes. Moreover, elevated preoperative PLR was associated with reduced ERAS adherence, implying its potential utility as a preoperative risk stratification marker.

These findings reinforce the clinical value of ERAS protocols and highlight the potential of integrating inflammatory biomarkers such as NLR and PLR into perioperative monitoring strategies. Their combined use may support early identification of patients at risk, enabling timely intervention and individualized postoperative care.

Future research should focus on validating these associations in larger, multicenter studies and defining optimal biomarker thresholds for clinical use. Establishing predictive models that incorporate these markers may improve outcome forecasting and protocol compliance in pancreatic surgery

Thesis synopsis

This prospective observational study examines the association between Enhanced Recovery After Surgery (ERAS) protocol compliance and specific postoperative inflammatory markers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients undergoing pancreatoduodenectomy for pancreatic cancer. The aim is to evaluate how ERAS adherence influences the surgical stress response and whether variations in these markers are linked to the development of severe postoperative complications.

Pancreatoduodenectomy is a complex procedure with a high rate of morbidity due to the physiological stress it causes. ERAS protocols are designed to minimize this stress and promote recovery through a multimodal, evidence-based perioperative approach. Inflammatory markers such as NLR and PLR are increasingly recognized as accessible indicators of surgical stress and immune response. However, their role in the context of ERAS compliance and clinical outcomes after major pancreatic surgery remains unclear.

The study was conducted in two Greek hospitals and included 92 patients undergoing elective open pancreatoduodenectomy within an ERAS framework. Compliance was measured using a 20-point checklist, and NLR and PLR values were recorded preoperatively and daily up to postoperative day five. Statistical analysis was performed using R and JASP software, with multivariate regression and correlation tests applied to explore relationships between ERAS adherence, biomarker changes, and complications.

Preliminary results suggest that higher ERAS compliance is associated with early elevations in NLR and PLR—likely reflecting a prompt immune response—while patients who developed severe complications had significantly lower values, possibly indicating immunosuppression. Additionally, elevated preoperative PLR correlated with reduced ERAS adherence, highlighting its potential prognostic value.

These findings support the utility of NLR and PLR as simple, cost-effective biomarkers for monitoring surgical stress and guiding clinical decision-making in pancreatic surgery. Ethical approval was obtained from all relevant institutional bodies, and informed consent was collected from all participants. Further research is needed to validate these associations and define predictive thresholds for clinical use.

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