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ANTERO DO VALE FERNANDES

COMO MITIGAR O RISCO PERIOPERATÓRIO EM CIRURGIA DIGESTIVA ONCOLÓGICA?

Tese de Candidatura ao grau de Doutor em Ciências Médicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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As opiniões expressas no presente trabalho de investigação são da exclusiva responsabilidade do seu autor.

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Sonho que sou alguém cá neste mundo …
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Aos pés de quem a Terra anda curvada.
E quando mais no Céu eu vou voando,
E quando mais no alto ando voando,
Acordo do meu sonho … E não sou nada!

Florbela Espanca
(Poetisa: 1984 - 1930)

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PRINCIPAIS ABREVIATURAS, SIGLAS E SINAIS UTILIZADAS

ACS NSQIP	American College of Surgeons National Surgical Quality Improvement Program
ACC	American College of Cardiology
AHA	American Heart Association
AEx	Aerobic exercise
AHRF	Acute hypoxemic respiratory failure
AMIB	Associação de Medicina Intensiva Brasileira
ANOVA	Analysis of variance
APACHE	Acute Physiology, Age, Chronic Health Evaluation
ARISCAT	Perioperative score for pulmonary complications
ARDS	Acute Distress Respiratory Syndrome
AS	Abdominal surgery
ARSLVT	Administração Regional de Saúde de Lisboa e Vale do Tejo
ASA PS	American Society of Anesthesiologists Physical Status Classification
ATHENEU	Editora
AVC	Acidente Vascular Cerebral
BiPAP	Bilevel Positive Pressure Airway
BMI	Body mass index
BSc	Bachelor of Science
CdtC	Circuito do doente crítico
CCI	Comprehensive Complication Index
CCD	Classificação de Clavien-Dindo
CCVP	Complicações cardiovasculares pós-operatórias
CECC	Cancro espinocelular da cabeça e pescoço
CGI	Cancro gastrointestinal
CID	Classificação internacional de doenças
CEOMMI	Colégio de Especialidade da Ordem dos Médicos - Medicina Intensiva
CONT	Control
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous positive airway pressure
CPO	Complicações pós-operatórias
CPP	Complicações pulmonares pós-operatórias
CGI	Cancro gastrintestinal
C&P	Cabeça & Pescoço

Cst	Static Compliance
Cdin	Dynamic Compliance
DGS	Direção Geral de Saúde
DiCE	Digestive Cancers Europe
Doi	Digital Object Identifier
DPOC	Doença Pulmonar Obstrutiva Crónica
DTPL	NCCN Distress Thermometer and Problem List
ECTS	Sistema Europeu de Transferência de Créditos
EDIC	European Diploma in Intensive Care
EECAM	European Intestine Cancer Month
EMAPO	Estudo Multicêntrico de Avaliação Perioperatória
EORTC	European Organization for Research and Treatment of Cancer
E.P.E.	Entidade Pública Empresarial
ERJ	European Respiratory Journal
ESICM	European Society of Intensive Care Medicine
FCT	Fundação para a Ciência e Tecnologia
FDM	Fundamental Disaster Management
FiO2	Inspiratory oxygen fraction
FLOT	5-fluorouracil, Oxaliplatin, Leucovorin and Docetaxel
GBD	Global Burden Disease
GEJ	Gastroesophageal junction
Google Scholar	Full text or metadata of scholarly literature
HFNC	High-flow nasal cannula
HGO	Hospital Garcia de Orta
h-index	Index of scientific research impact
HIPEC	Quimioterapia intraperitoneal hipertérmica
H&N	Head & Neck
https	Hypertext Transfer Protocol Secure
ICC	Insuficiência cardíaca congestiva
ICU	Intensive Care Unit
IHME	Institute for Health Metrics and Evaluation
INE	Instituto Nacional de Estatística
INEM	Instituto Nacional de Emergência Médica
IPO FG	Instituto Português de Oncologia Francisco Gentil
IRA	Insuficiência Respiratória Aguda
IRHA	Insuficiência respiratória hipoxémica aguda
IST	Instituto Superior Técnico
I-TIS	Intraoperative Therapeutic Intervention Score
TI	Tracheal intubation
JGE	Junção gastroesofágica
JIF	Journal Impact Factor
LAQV	Laboratório Associado para Química Verde
LPC	Laparoscopy
LPT	Laparotomy

MAE	Mean Absolute Error
MAPE	Mean absolute percentage error
MEDLINE	Medical Literature Analysis and Retrieval System Online
MERS	Middle East Respiratory Syndrome
NMBD	Neuromuscular blocking drugs
NAC	Neoadjuvant chemotherapy
NLM	United States National Library of Medicine
M.Sc.	Master Degree
M.D	Medical Doctor
NIPPV	Non Invasive Positive Pressure Ventilation
ONCOCIR	Education and Care in Oncology, Lusophone Africa
ONCOL	Oncology
OMS	Organização Mundial de Saúde
OP	Operated patients
PaO_2	Arterial oxygen pressure
P_aCO_2	Arterial carbon dioxide pressure
PAO_2	Alveolar oxygen pressure
PALOPs	Países Africanos de Língua Oficial Portuguesa
PAV	Pneumonia associada ao ventilador
PERISCOPE	Predicting post-operative pulmonary complications in Europe
POC	Postoperative complications
PCR	Paragem cardiorrespiratória
PCR	Proteína C reativa
PCT	Perioperative chemotherapy
PEEP	Positive end-expiratory pressure
PICU	Polyvalent Intensive care unit
PG-SGA	Patient Generated Subjective Global Assessment
Ph.D.	Philosophiae Doctor
POC	Postoperative Complications
POMS	Postoperative Morbidity Survey
PPC	Postoperative pulmonary complications
P-POSSUM	Operative Severity Score for the enumeration of Mortality
PÓS-DOC	Pós-doutoramento
POSA	Preoperative serum albumin
PPC	Postoperative pulmonary complications
PERISCOPE	Prospective Evaluation of a Risk Score for Postoperative Pulmonary Complications in Europe
PMID	Link from life sciences and biomedical articles to PubMed.
PREOP	Preoperative period
PREHAB	Prehabilitation
PubMed	Free search engine accessing primarily the MEDLINE database
QLQ-C30	Quality of Life Questionnaire Core-30
QNA	Quimioterapia neoadjuvante
Qs/Qt	Shunt equation

REF	Research Excellence Framework
REQUIMTE	Rede de Química e Tecnologia
RON	Registo Oncológico Nacional
RMSE	Root Mean Square Error
RORENO	Registo Oncológico da Região Norte
SAC	Síndrome de anorexia-caquexia
SAPS	Simplified Acute Physiology Score
SARS	Severe Acute Respiratory Syndrome
SciELO	Scientific Electronic Library Online
SDRA	Síndrome da Dificuldade Respiratória do Adulto
SMI	Serviço de Medicina Intensiva
SMR	Standardized Mortality Rate
SOFA	Sequential Organ Failure Assessment Score
SPG	Sociedade Portuguesa de Gastrenterologia
SPCI	Sociedade Portuguesa de Cuidados Intensivos
SRC	Surgical Risk Calculator
SUG	Serviço de urgência geral
SCCM	Society of Critical Care Medicine
SciELO	Scientific Electronic Library Online
SIDA	Síndrome de Imunodeficiência Adquirida
SMI	Serviço de Medicina Intensiva
SNS	Serviço Nacional de Saúde
SPCI	Sociedade Portuguesa de Cuidados Intensivos
SPIRIT	Recommendations for Interventional Trials
SPSS	Statistical Package for the Social Sciences
SRC	Surgical Risk Calculator
TISS	Therapeutic intervention scoring system
UCI	Unidade de Cuidados Intensivos
UCIM	Unidade de Cuidados Intensivos Médicos
UCIP	Unidade de Cuidados Intensivos Polivalentes
USA	United States of America
VAP	Ventilator-associated pneumonia
VIH	Vírus de Imunodeficiência Humana
VNI	Ventilação Não Invasiva
VPPNI	Ventilação por Pressão Positiva Não Invasiva
Vol	Volume
Vt	Volume tidal
Vol_{min}	Volume minuto

- As abreviaturas utilizadas nos trabalhos originais estão legendadas nos respetivos artigos

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RESUMO

Introdução e objetivos: Apesar do seu papel central no tratamento dos tumores sólidos, a cirurgia oncológica não é isenta de efeitos adversos, com as complicações pós-operatórias (CPO) a assumirem-se como uma importante causa de morbilidade e mortalidade, particularmente em doentes de alto risco. Estima-se que cerca de 50% das CPO poderão ser prevenidas, o que tem motivado múltiplos esforços para compreender melhor esta problemática. É fundamental conhecer as suas causas, caracterizar o perfil dos doentes mais susceptíveis e identificar precocemente esses mesmos doentes, sendo também imperativo identificar estratégias eficazes de prevenção e de mitigação de risco. Pese embora alguns avanços registados a nível internacional, a reduzida validade externa do conhecimento gerado é frequentemente uma limitação à sua extrapolação para populações diferentes daquelas em que a evidência foi gerada. Assim, consideramos apropriado caracterizar melhor a realidade da cirurgia digestiva oncológica em Portugal, tendo sido estabelecidos os seguintes objetivos: 1) Comparar a precisão de ferramentas de avaliação de risco cirúrgico na predição de complicações pós-operatórias em doentes do foro de oncologia digestiva e propor um novo instrumento de previsão de risco cirúrgico mais proficiente e adaptado à nossa realidade; 2) Caracterizar os fatores de risco perioperatórios para as complicações pulmonares de doentes submetidos a cirurgia abdominal e avaliar a sua associação com a morbilidade e mortalidade pós-operatória; 3) Elaborar uma proposta de mitigação do risco de complicações pós-operatórias através da pré-habilitação. Metodologia: Para responder ao primeiro objetivo, realizamos um estudo de coorte observacional e retrospetivo com 345 doentes oncológicos admitidos na unidade de cuidados intermédios cirúrgicos do Instituto Português de Oncologia (IPO-Porto) no período de janeiro de 2016 a abril de 2018, após cirurgia de cancro gastrointestinal (81,5% eletivos e 18,5% urgentes). Para o segundo objetivo, realizamos um estudo, também de coorte observacional e retrospetivo, no Hospital Garcia de Orta, Almada,

Portugal, tendo sido estudados 60 doentes submetidos a cirurgia abdominal urgente ou eletiva, que desenvolveram complicações pulmonares no período pós-operatório, motivo pelo qual foram internados na UCIP, entre janeiro a dezembro de 2017. Para concretizar o terceiro objetivo, promovemos o papel da pré-habilitação cirúrgica, enquanto estratégia multimodal de otimização pré-operatória em doentes de alto risco, através de i) um Essay dirigido às necessidades da população cirúrgica na África Subsaariana e ii) uma proposta para a realização de um ensaio clínico randomizado. Resultados: Os resultados do primeiro estudo revelaram que a precisão e concordância das ferramentas de avaliação do risco cirúrgico utilizadas para a predição de complicações pós-operatórias são limitadas. Com base nas variáveis mais informativas das ferramentas estudadas, desenvolvemos um novo modelo de predição de risco cirúrgico, o MyIPOrisk-score, que demonstrou ter maior capacidade de discriminação do que o obtido com cada instrumento previamente utilizado. Os resultados do segundo estudo sugerem que as complicações pulmonares após cirurgia abdominal são frequentes, e têm um impacto profundo no prognóstico. Destaca-se ainda a observação de que os doentes com elevado risco pré-operatório que foram alvo de alguma otimização antes da cirurgia apresentaram menos necessidade de ventilação mecânica no tratamento das complicações respiratórias, corroborando a importância do periodo pré-operatório para implementar estratégias de mitigação de complicações pós-operatórias e de diminuição da mortalidade. Nessa sequência, destacamos o papel da pré-habilitação, o qual foi concretizado na reflexão apresentada no Essay e na proposta de ensaio clínico dirigida a doentes com adenocarcinoma esofáfico ou do estômago localmente avançado.

Conclusão: Em termos gerais, os principais resultados da nossa investigação evidenciam que as CPO constituem um problema importante em Portugal, sendo que a sua mitigação passará necessariamente pela identificação dos doentes com risco cirúrgico mais elevado, individualização dos cuidados pré-operatórios (ex: pré-habilitação multimodal) e antecipação/planeamento de cuidados pós-operatórios (ex: necessidade de suporte ventilatório).

ABSTRACT

Introduction and objectives: Despite its central role in the treatment of solid tumors, cancer surgery is not without adverse effects, with postoperative complications (POC) becoming a significant cause of morbidity and mortality, particularly in patients' high risk. It is estimated that around 50% of POC can be prevented, which has motivated multiple efforts to understand this problem better. It is essential to know their causes, to characterize the profile of the most susceptible patients and to identify these same patients early. It is also imperative to identify effective prevention and risk mitigation strategies. Despite some advances at the international level, the limited external validity of the knowledge generated is often a limitation to its extrapolation to populations other than those in which the evidence was forged. Thus, we consider it appropriate better to characterize the reality of oncological digestive surgery in Portugal, having established the following objectives: 1) To compare the precision of surgical risk assessment tools in the prediction of postoperative complications in patients of the digestive oncology patients and to propose a new instrument for predicting the surgical risk that is more proficient and adapted to our reality; 2) To characterize the perioperative risk factors for pulmonary complications in patients undergoing abdominal surgery and to evaluate their association with postoperative morbidity and mortality; 3) Develop a proposal to mitigate the risk of postoperative complications through pre-habilitation. Methodology: To answer the first objective, we carried out an observational and retrospective cohort study with 345 cancer patients admitted to the surgical intermediate care unit of the Portuguese Institute of Oncology (IPO-Porto) from January 2016 to April 2018, after gastrointestinal surgery cancer (81.5% elective and 18.5% urgent). For the second objective, we carried out a study, also of an observational and retrospective cohort, at Hospital Garcia de Orta, Almada, Portugal, having studied 60 patients undergoing urgent or elective abdominal surgery, who developed pulmonary complications in the postoperative period, which is the

reason for which they were admitted to the PICU, between January and December 2017. To achieve the third objective, we promoted the role of surgical pre-habilitation, as a multimodal strategy for preoperative optimization in high-risk patients, through i) an Essay directed the needs of the surgical population in sub-Saharan Africa and ii) a proposal for a randomized clinical trial. Results: The results of the first study revealed that the precision and agreement of the surgical risk assessment tools used to predict postoperative complications are limited. Based on the most informative variables of the devices studied, we developed a new model of surgical risk prediction, the MyIPOrisk-score, which demonstrated greater discrimination capacity than that obtained with each previously used instrument. The results of the second study suggest that pulmonary complications after abdominal surgery are frequent and have a profound impact on prognosis. It should also be noted that patients with high preoperative risk who underwent some optimization before surgery had less need for mechanical ventilation in the treatment of respiratory complications, corroborating the importance of the preoperative period to implement mitigation strategies, postoperative complications and decreased mortality. In this sequence, we highlight the role of pre-habilitation, which was realized in the reflection presented in Essay and the proposal for a clinical trial aimed at patients with oesophagal adenocarcinoma or locally advanced stomach.

Conclusion: In general terms, the main results of our investigation show that POC is a fundamental problem in Portugal, and their mitigation will necessarily involve the identification of patients at higher surgical risk, individualization of preoperative care (ex: multimodal prehabilitation) and anticipation/planning of postoperative care (e.g., need for ventilatory support).

ARTIGOS PUBLICADOS/SUBMETIDOS EM RELAÇÃO COM A INVESTIGAÇÃO BASE DO CICLO DE DOUTORAMENTO

PUBLICAÇÕES CIENTÍFICAS EM PRIMEIRA AUTORIA

1. **Antero Fernandes**, MD; Jéssica Rodrigues, MSc Mat; Luís Antunes, PhD Mat; Patrícia Lages, MD; Carla Salomé Santos, BSW; Daniel Moreira Gonçalves, PhD; Rafael S. Costa, PhD; Joaquim Abreu Sousa, MD; Mário Dinis-Ribeiro, PhD; Lucio Lara Santos, PhD.

   Development of a preoperative risk score on admission in surgical intermediate care unit in gastrointestinal cancer surgery. *Perioperative Medicine* (2020) 9: 23. https://doi.org/10.1186/s13741-020-00151-7.
   PMID: 32774846, JIF: 2.740

2. **Antero Fernandes**, MD; Jéssica Rocha Rodrigues, MSc; Patrícia Lages, MD; Sara Lança, MD; Paula Mendes, MD; Luís Antunes, PhD; Carla Salomé Santos, BSc; Clara Castro, PhD; Rafael S. Costa, PhD; Carlos Silva Lopes, PhD, MD; Paulo Matos Costa, PhD, MD; Lucio Lara Santos, PhD, MD.

   Root causes and outcomes of postoperative pulmonary complications after abdominal surgery: a retrospective observational cohort study. *Patient Safety in Surgery* 13(1) • December 2019. https://doi.org/10.1186/s13037-019-0221-5
   PMID: 31827617, JIF: 1.26

3. **Antero do Vale Fernandes**, MD, EDIC, Daniel Gonçalves, PhD, Paulo Matos da Costa, MD, MSc, PhD, Lúcio Lara Santos, MD, MSc, PhD.

   Prehabilitation program for African Sub-Saharan surgical patients is an unmet need? *Pan African-Med-Journal*, Volume 36, Article 62, 03 Jun 2020 | 10.11604 / pamj.2020.36.62.21203.
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4. **Antero do Vale Fernandes**, Daniel Moreira-Gonçalves and Lúcio Lara Santos.

   A home-based prehabilitation program, delivered through an internet-based platform, in patients with locally advanced gastric or esophageal adenocarcinoma, undergoing perioperative chemotherapy with FLOT regimen: protocol for a feasibility and acceptability study of a multicentric, randomized, control trial. Submetido para publicação à *Revista Portuguesa de Cirurgia*.
   Metrics: SciELO e Google Scholar – 2017: h5 index: 3, h5 median: 8

PUBLICAÇÕES CIENTÍFICAS EM COAUTORIA

1. Ana Sousa Menezes, **Antero Fernandes**, Jéssica Rocha Rodrigues, Carla Salomé, Firmino Machado, Luís Antunes, Joaquim Castro Silva, Eurico Monteiro, Lúcio Lara Santos.

   Optimizing classical risk scores to predict complications in Head and Neck surgery: a new approach. *European Archives of Oto-Rhino-Laryngology* https://doi.org/10.1007/s00405-020-06133-1
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Capítulo I - INTRODUÇÃO

1.1 Epidemiologia das neoplasias malignas no mundo e em Portugal

As neoplasias malignas constituem um dos mais importantes problemas de saúde pública mundial [1], com os registos de cancro de base populacional a ilustrarem um aumento da sua incidência em todo o mundo [2]. De facto, desde o final do século XX que se tem vindo a assistir a um crescimento progressivo do número de novos casos anuais de neoplasias malignas, bem como o aumento da mortalidade por cancro [3]. Em 2018 foram estimados 18,1 milhões de novos casos e 9,6 milhões de mortes, com as neoplasias malignas a ocuparem a segunda posição enquanto causa de morte por doença não comunicável no mundo [1]. A OMS prevê que em 2030 as neoplasias ultrapassarão a doença isquémica, tornando-se a principal causa de morte em todo o mundo, sendo responsáveis por 18,5% de todas as mortes [4].

Para ambos os sexos combinados, o cancro do pulmão foi o mais diagnosticado (11,6% do total de novos casos), seguido de perto pelo cancro da mama feminino (11,6%), colorretal (10,2%) e próstata (7,1%). Em termos de mortalidade, o cancro do pulmão continua a liderar (18,4% do total de mortes cancro), seguindo-se o cancro colorretal (9,2%), estômago (8,2%) e fígado (8,2%) [1]. As estimativas epidemiológicas sugerem ainda que os números serão progressivamente mais preocupantes nos próximos anos, com as projeções a apontarem para cerca de 22,2 milhões de novos casos em 2030 (12,7 milhões em 2008) e 13,2 milhões de mortes (7,6 milhões em 2008) [5]. Esta tendência reflete não só a transição demográfica atual (o envelhecimento e o crescimento populacional), mas também a adoção de comportamentos que aumentam o risco de cancro [3], bem como a maior disponibilidade de meios para efetuar diagnósticos e rastreios [6, 7].

São reconhecidas importantes diferenças epidemiológicas relativas à incidência e mortalidade das neoplasias malignas quanto ao género. O cancro do pulmão é o mais diagnosticado (1,4 milhões) e a principal causa de morte por cancro nos homens (1,2 milhões), seguido pelo cancro da próstata (1,3 milhões) e colorretal (1 milhão) para incidência e o cancro do fígado (548 mil) e estômago (514 mil) para mortalidade. Já para as mulheres, o cancro de mama foi o mais diagnosticado em 2018 (2 milhões) e a principal causa de morte por cancro (627 mil), seguido pelo cancro colorretal (795 mil) e pulmão (725 mil) para incidência e cancro do pulmão (576 mil) e colorretal (387 mil) para a mortalidade, com o cancro do colo do útero a ocupar o quarto lugar em termos de incidência e mortalidade [1]. Destacam-se ainda algumas variações na incidência e mortalidade entre diferentes regiões geográficas e entre países de renda baixa/média versus renda elevada. Apesar da menor incidência de doença neoplásica, cerca de 65% da mortalidade associada ocorre nos países de baixa e média renda em comparação com os países de alta renda, afetando particularmente indivíduos com menos de 65 anos de idade [8]. Os motivos desta discrepância incluem diferenças relativas a modos de vida e padrões de consumo que afetam a prevalência e distribuição dos principais fatores de risco (ex: sedentarismo, obesidade, alimentação, tabaco, álcool, infeções persistentes por Helicobacter Pylori, Vírus da Hepatite B e Vírus do Papiloma Humano), educação (ex: sobre sintomas) ou limitações ao nível do acesso a serviços de diagnóstico e tratamento de qualidade [9]. De acordo com a OMS, em 2017, mais de 90% dos países de alta renda possuíam serviços de tratamento disponíveis, em comparação com menos de 30% dos países de baixa renda [10]. De destacar ainda o facto de que o impacto nos países de baixa renda poderá ser mais grave, uma vez que os registos oncológicos e sistemas de reporte são raros e/ou pouco rigorosos [11]. O enorme impacto económico da mortalidade prematura e a perda de anos de vida produtiva impõem a necessidade de desenvolver e implementar estratégias de prevenção, sem descurar o esforço na gestão dos recursos necessários para garantir, paralelamente, o desenvolvimento sustentável desses países [8]. Adicionalmente, é importante lembrar que o sucesso da deteção precoce ficará condicionado a jusante pela disponibilidade de recursos e de acesso a terapia multimodal adequada, pelo que se antecipam desafios sem

precedentes sobre a sociedade, saúde e economia nos países de baixa e média renda, já por si frágil [8].

Em Portugal, segundo dados da Direção Geral da Saúde (DGS) e em consonância com a tendência a nível mundial, a incidência de cancro tem aumentado 3-4% ao ano, sendo que em 2015 foram registados cerca de 50 mil novos casos [12]. Num relatório divulgado em 2018, a OMS, através da Agência Internacional para a Investigação do Cancro, afirmou que um quarto da população portuguesa estaria em risco de desenvolver cancro até aos 75 anos e 10% corria na altura o risco de morrer de doença oncológica [13]. À semelhança do que se passa noutros pontos do globo, os ganhos na esperança de vida da população portuguesa (Figura 1), bem como as modificações dos estilos de vida parecem ser os principais fatores a influenciar as variações da incidência de neoplasias malignas e contribuir para mudanças relativas entre as mesmas.

Figura 1. Estrutura da pirâmide populacional em Portugal em 2015 e previsão para 2030 e 2060. Fonte: Direção-Geral da Saúde [12]

A conjugação destes dois fatores condiciona uma previsão em alta da evolução da incidência das neoplasias malignas, estimando-se que em 2030, possa ser atingido a cifra de 60 mil novos casos em Portugal (Figura 2) [13].

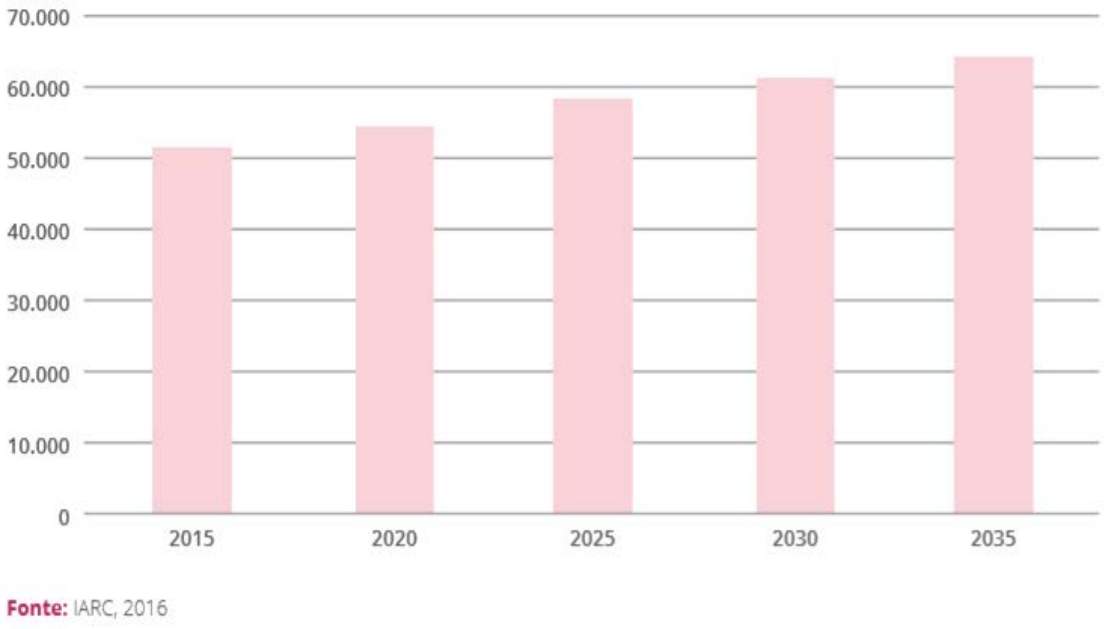

Figura 2. Previsão da evolução da incidência de cancro em Portugal (2015-2035).
Fonte: Direção-Geral da Saúde [12]

No que concerne ao tipo específico de tumor maligno, os tumores da próstata, mama e cólon, constituem as neoplasias malignas com maior incidência global em Portugal (Tabela 1) [12].

Tabela 1. Taxa de incidência de tumores malignos (por 100 000 habitantes)

TAXA DE INCIDÊNCIA DE TUMORES MALIGNOS (100000 HABITANTES)		
	Taxa bruta	Taxa pad. (pop. Eur.)
Próstata	120,3	90,5
Mama	62,5	50,2
Cólon	47,6	32,1
Traqueia, Brônquios e Pulmão	35,8	26,5
Estômago	27,8	18,9
Reto	22,7	15,8
Corpo do Útero	17,8	12,4
Bexiga	17,3	11,3
Linfoma não Hodgkin	17,1	12,9
Glândula Tiroideia	15,3	13,7
Total	444,5	330,3

Fonte: RORENO, RON 2010

Fonte: Direção-Geral da Saúde [12]

Podemos verificar diferenças significativas de incidência em termos de distruibuição por género, em alguns dos principais tumores malignos em Portugal. Se compararmos apenas os três tumores malignos mais incidentes, verifica-se que os tumores da próstata, do sistema respiratório (traqueia, bronquios e pulmão), cólon e estômago são os mais incidentes no sexo masculino, enquanto que para o sexo feminino se destacam os tumores da mama, cólon, glandula tiroideia e estômago (Tabelas 2 e 3).

Tabela 2. Taxa de incidência de tumores malignos, (por 100.000), no sexo masculino (2010) [12]

	Taxa bruta	Taxa pad. (pop. Eur.)
Próstata	120,3	90,5
Traqueia, Brônquios e Pulmão	57,7	45,2
Cólon	57,1	42,3
Estômago	34,8	26,2
Reto	29,7	22,6
Bexiga	27,9	20,4
Linfoma não Hodgkin	19,2	15,4
Rim	12,6	10,2
Laringe	11,7	9,9
Esófago	9,3	7,7
Total	512,0	398,8

Fonte: RORENO, RON 2010

Tabela 3. Taxa de incidência de tumores malignos, (por 100.000), no sexo feminino (2010)

	Taxa bruta	Taxa pad. (pop. Eur.)
Mama	118,5	93,2
Cólon	39,0	24,2
Glândula Tiroideia	23,8	21,5
Estômago	21,3	13,1
Corpo do Útero	17,8	12,4
Reto	16,3	10,4
Traqueia, Brônquios e Pulmão	15,8	11,0
Linfoma não Hodgkin	15,3	10,8
Colo do Útero	13,5	11,3
Melanoma Maligno da Pele	9,1	6,9
Total	382,7	279,6

Relativamente à mortalidade, o Instituto Nacional de Estatística (INE), no seu relatório anual sobre causas da morte no ano de 2017, enfatiza a importância do cancro em Portugal, dando-nos conta de que os portugueses morrem sobretudo de doenças cardíacas e tumores malignos, representando estas duas causas de morte mais de metade dos 110 mil óbitos registados no País no referido ano [14]. Em conjunto, estes dois grupos de causas foram responsáveis por 54,4% dos óbitos, levando-nos a concluir que a mortalidade associada aos tumores malignos em Portugal continua muito significativa [14]. De facto, se a mortalidade associada às doenças do aparelho circulatório tem tendência para diminuir (atingindo mesmo assim 29,4% do total), o número de óbitos relacionados com tumores malignos apresenta uma trajetória ascendente, sendo já responsável por 25% das mortes (Figura 3) [12].

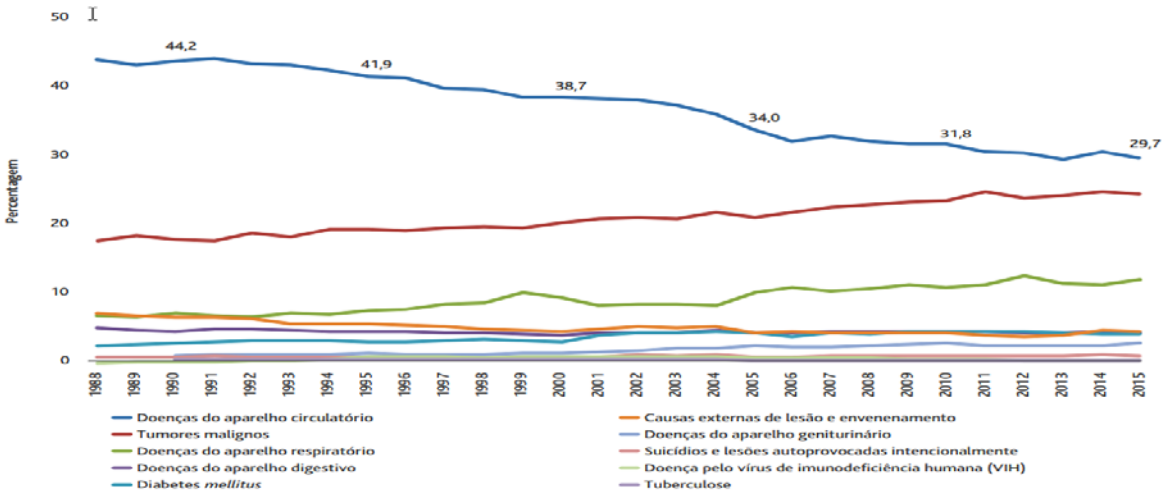

Figura 3. Evolução da proporção de óbitos pelas principais causas de morte no total das causas de morte em Portugal (%), 1988 a 2015.
Fonte: Direção-Geral da Saúde [12]

Fazendo uma avaliação do contributo de 36 tipos de doença oncológica para a mortalidade em Portugal, a OMS reporta que o cancro do pulmão é o mais mortal, tal como acontece a nível mundial, seguido do cancro do cólon, do estômago e da próstata, ocupando o cancro da mama o quinto lugar [13]. Destacaríamos nesta altura o cancro gastrointestinal (CGI), enfoque particular da nossa investigação, que compreende o conjunto de tumores malignos que

afetam o sistema digestivo, interferem fortemente com a qualidade de vida dos cidadãos e têm uma elevada taxa de mortalidade. Esófago, estômago, pâncreas, fígado, cólon e reto são os cinco principais órgãos do aparelho digestivo onde incide o cancro digestivo, dois dos quais (pâncreas e fígado) são dos mais mortais e com esperança média de vida inferior a um ano. Em 30 de setembro de 2019, dia nacional contra o cancro digestivo, a Sociedade Portuguesa de Gastrenterologia (SPG), ao analisar o panorama atual do cancro digestivo em Portugal, destaca que cerca de um terço das mortes por cancro se encontram relacionadas com o aparelho digestivo, o que se traduz em cerca de 10 mil por ano, ou seja, 30 por dia, cerca de 1 por hora. Este número tem vindo a aumentar nos últimos anos, representando um grave problema de saúde pública, responsável por cerca de 10% da mortalidade Portuguesa [15]. Nas tabelas 4, 5 e 6 são apresentados os indicadores de mortalidade e distribuição por género relativos a neoplasias malignas do aparelho digestivo, em particular do estômago, cólon, junção retosigmóide e reto. Com um diagnóstico e tratamento precoces e com as novas armas terapêuticas disponíveis será possível aumentar a sobrevivência destes doentes.

Tabela 4. Indicadores de mortalidade relativos a tumor maligno do estômago, em Portugal (2010-2014) [12]

TUMOR MALIGNO DO ESTÔMAGO					
	2010	2011	2012	2013	2014
AMBOS OS SEXOS					
Número de óbitos	2.318	2.428	2.371	2.265	2.290
Taxa de mortalidade	21,8	23,0	22,6	21,7	22,0
Taxa de mortalidade padronizada	14,4	14,5	14,0	13,2	13,1
SEXO MASCULINO					
Número de óbitos	1.375	1.491	1.424	1.349	1.381
Taxa de mortalidade	26,7	29,6	28,4	27,1	27,9
Taxa de mortalidade padronizada	20,2	21,1	20,0	18,8	18,7
SEXO FEMININO					
Número de óbitos	943	937	947	916	909
Taxa de mortalidade	17,2	17,0	17,2	16,7	16,6
Taxa de mortalidade padronizada	9,7	9,4	9,3	8,9	8,8

Taxas: por 100.000 habitantes. Códigos da CID-10: C 16.
Fontes: INE, 2016

Tabela 5. Indicadores de mortalidade relativos a tumor maligno do colón, por sexo, em Portugal (2010-2014)

TUMOR MALIGNO DO CÓLON					
	2010	2011	2012	2013	2014
AMBOS OS SEXOS					
Número de óbitos	2.647	2.740	2.686	2.724	2.687
Taxa de mortalidade	25,0	26,0	25,6	26,1	25,8
Taxa de mortalidade padronizada	15,4	15,5	14,9	15,0	14,5
SEXO MASCULINO					
Número de óbitos	1.511	1.500	1.533	1.560	1.526
Taxa de mortalidade	29,9	29,8	30,6	31,4	30,9
Taxa de mortalidade padronizada	21,0	20,5	20,4	20,5	19,7
SEXO FEMININO					
Número de óbitos	1.136	1.240	1.153	1.164	1.161
Taxa de mortalidade	20,6	22,5	21,0	21,2	21,3
Taxa de mortalidade padronizada	11,2	11,8	11,0	11,1	10,7

Taxas: por 100.000 habitantes. Códigos da CID 10: C 18.
Fontes: INE, 2016

Fonte: Direção-Geral da Saúde [12]

Tabela 6. Indicadores de mortalidade relativos a tumor maligno da junção retosigmóide e do reto, por sexo, em Portugal (201-2014)

TUMOR MALIGNO DA JUNÇÃO RETOSSIGMÓIDE E DO RETO					
	2010	2011	2012	2013	2014
AMBOS OS SEXOS					
Número de óbitos	1.084	1.051	1.088	1.079	1.073
Taxa de mortalidade	10,3	10,0	10,4	10,3	10,3
Taxa de mortalidade padronizada	6,5	6,1	6,2	6,1	6,0
SEXO MASCULINO					
Número de óbitos	703	661	689	653	655
Taxa de mortalidade	13,9	13,1	13,7	13,1	13,3
Taxa de mortalidade padronizada	9,9	9,2	9,3	8,9	8,6
SEXO FEMININO					
Número de óbitos	381	390	399	426	418
Taxa de mortalidade	6,9	7,1	7,3	7,8	7,7
Taxa de mortalidade padronizada	4,0	3,8	4,0	4,0	4,0

Taxas: por 100.000 habitantes. Códigos da CID 10: C19-C20.
Fontes: INE, 2016

Fonte: Direção-Geral da Saúde [12]

Analisando as causas e o número de anos que teoricamente a população portuguesa deixa de viver quando morre antes dos 70 anos de idade (anos potenciais perdidos), para ambos os sexos, as causas neoplásicas, como os

tumores malignos da traqueia, brônquios e pulmão ocupam as posições cimeiras, em detrimento de outras causas, como por exemplo as doenças atribuíveis ao álcool e até as doenças isquémicas do coração muito prevalentes entre nós [12].

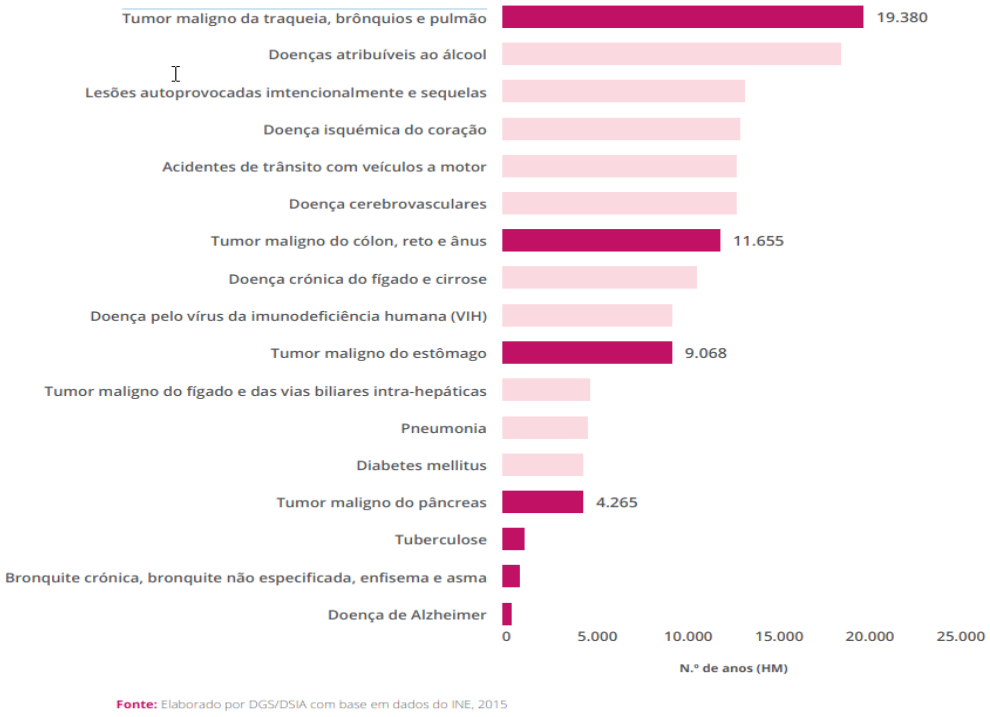

Figura 4. Anos potenciais de vida perdidos por causas de morte relacionadas, Portugal Continental (2013). Fonte: Direção-Geral da Saúde [12]

Em suma, as neoplasias malignas para além de serem uma doença do presente, são também uma doença do futuro e necessitam de uma abordagem clínica multidisciplinar, alicerçada numa perspetiva política e social concertada, que se deve estender para além dos muros das estruturas de saúde [5]. O seu perfil epidemiológico é um importante instrumento para gestores, profissionais da saúde e público em geral, trazendo contribuições para o planeamento das prioridades em termos de ações em saúde, principalmente no que tange à deteção precoce e tratamento oportuno. De facto, cerca de um terço dos 10 milhões de novos casos de cancro diagnosticados todos os anos a nível mundial podem ser prevenidos e outro terço curado, se forem detetados e tratados numa fase precoce [16-18]. A implementação e funcionamento dos rastreios

oncológicos de base populacional, para alguns tipos de neoplasias malignas, nomeadamente para os cancros da mama, do colo do útero e colo-retal de entre outros, ao permitirem a monitorização de uma forma organizada, tem sido muito importante para a execução de programas específicos, onde esta informação é particularmente relevante. A título de exemplo, este facto pode conduzir ao desenvolvimento de mecanismos que permitam responder, de forma mais documentada, às diferenças que são determinadas pelo dimorfismo sexual e, simultaneamente, minorar ou eliminar as iniquidades tecidas a partir deste, não se tratando, contudo, de uma forma de intervenção em universos separados, uma vez que, nesta matéria, os fenómenos físicos mentais e sociais interagem de forma demasiado complexa para que, sobre eles, se estabeleçam grelhas de leitura estanques e estereotipadas [19].

1.2 Tratamento cirúrgico em oncologia

A oncologia é a medicina das neoplasias malignas, não havendo como separar o tratamento médico do tratamento cirúrgico. A cirurgia é a forma mais antiga de tratamento do cancro e pode assumir um caráter preventivo, diagnóstico, de estadiamento, curativo, de suporte e restaurador [20]. Além disso, pode-se lançar mão da cirurgia para tratamento de eventuais complicações de neoplasias malignas em estádios avançados onde o objetivo é a melhoria de sintomas e oferecer melhor qualidade de vida ao doente quando não há perspetiva de cura [20].

Estima-se que aproximadamente 80% dos doentes com cancro, em algum momento do seu percurso, terão necessidade de tratamento cirúrgico, sendo que alguns deles serão submetidos a múltiplas intervenções cirúrgicas. No caso dos tumores sólidos precocemente diagnosticados, a ressecção cirúrgica, isoladamente ou em combinação com outras terapias como quimioterapia e radioterapia, aumenta significativamente as possibilidades de cura [20]. Curiosamente, apesar do seu papel terapêutico central, é difícil saber com exatidão qual o real impacto que a cirurgia com intenção curativa, por si só, tem sobre os ganhos de vida após diagnóstico. De facto, a informação proveniente de estudos observacionais encontra-se limitada por vários vieses

(particularmente o viés de seleção dos doentes) [20]. Do lado dos estudos randomizados, os ensaios clínicos das últimas décadas têm-se focado na eficácia de cirurgias menos agressivas/extensas (ex: lumpectomia versus mastectomia) [21, 22], no procedimento cirúrgico (ex: laparoscopia versus laparotomia) [23, 24], otimização de métodos cirúrgicos para administração de quimioterapia [25] ou sobre o impacto da remoção do gânglio sentinela [26]. Numa análise retrospetiva de dados de sobrevivência ajustada para o estádio de doentes diagnosticados nos anos 80 e no início dos anos 90, altura em que o tratamento não-cirúrgico não era prática comum, estimou-se que o tratamento cirúrgico por si só foi responsável por um incremento de 30-55% na sobrevida de doentes com cancro da mama (a 5 anos) e colorectal (a 3 anos) [20].

Em termos de volume de cirurgia geral, estima-se que em 2012 tenham sido realizadas em todo o mundo 313 milhões de cirurgias major, o que representa um crescimento de 38% face 2004, sendo que apenas 1 em cada 20 cirurgias foi realizada em países de baixa renda [27]. Apesar destes avanços, cerca de 5 bilhões de pessoas carecem de acesso a cuidados cirúrgicos e anestésicos seguros, acessíveis e oportunos, particularmente em países de baixo índice de desenvolvimento humano no Médio Oriente, Ásia-Pacífico, África e América Central, regiões onde 90% dos indivíduos não conseguem sequer obter cuidados cirúrgicos considerados básicos [28, 29]. Como consequência, um número muito significativo de pessoas morre pela falta de tratamento cirúrgico, o que representou 33% de todas as mortes no mundo em 2010 [29]. Concretamente no contexto oncológico, prevê-se que em 2015 tenham sido necessárias, a nível global, 32 milhões de cirurgias, com as projeções a indicarem um incremento substancial até 2030, onde se antecipa que venham a ser necessárias 45 milhões de cirurgias [20]. Este incremento não é de estranhar face à tendência de evolução da incidência das neoplasias para os próximos anos. De sublinhar ainda que a necessidade do tratamento cirúrgico no contexto oncológico é transversal a todas as faixas etárias, sendo crescente até aos 30 anos e aplanando nas faixas etárias seguintes [20]. Nos países de elevado índice de desenvolvimento humano, a proporção de doentes oncológicos adultos admitidos que necessitam de receber algum tipo de tratamento cirúrgico varia de forma considerável com o tipo de cancro (25% para as admissões por tumores

ósseos até mais de 70% para todas as admissões por cancro da bexiga e mama) [20]. A nível global, uma vez mais, as necessidades de cirurgia oncológica não acompanham as oportunidades de acesso ao tratamento, estimando-se que, em todo o mundo, apenas 25% dos doentes oncológicos recebam cuidados cirúrgicos adequados, seguros, acessíveis e atempadamente [20].

1.3 Complicações pós-operatórias

1.3.1. Definição e classificação

Apesar das melhorias observadas nos últimos anos em termos de anestesia, técnicas cirúrgicas e cuidados perioperatórios, o tratamento cirúrgico, em termos gerais, continua a estar associado a importante risco de morbilidade e mortalidade, em grande parte devido ao desenvolvimento de complicações pós-operatórias (CPO) [30]. As CPO são definidas como uma segunda doença, inesperada, que ocorre até 30 dias após o procedimento, ou a exacerbação de uma mesma doença preexistente em decorrência da cirurgia [31]. Estima-se que cerca de 50% das CPO poderão ser prevenidas [32], pelo que o estudo das CPO (ex: do seu perfil, das suas causas, da sua prevenção e da redução do seu impacto no prognóstico do doente) ocupa um lugar de destaque na atualidade. Destaca-se também a relevância que as CPO assumem hoje em dia enquanto métrica de qualidade e segurança do tratamento cirúrgico. A comparação de taxas de complicações pós-operatórias observadas e esperadas por instituição hospitalar é um relevante critério de benchmarking e, a par do referido, o impacto das complicações pós-operatórias nos resultados finais ao nível da efetividade e da eficiência são muito importantes para a planificação de uma eventual concentração de esforços e planeamento de recursos [33, 34]. Alguns países, no intuito de prevenir e consequentemente melhorar os resultados pós-cirúrgicos, criaram sistemas de recompensa (modalidade pay-for-performance), no qual retêm o pagamento referente a complicações que ocorreram e que são consideradas evitáveis [35]. O objetivo é o de prevenir e melhorar os resultados operatórios, tornando-se para tal muito importante a consciencialização e a preocupação com as CPO, sobretudo no contexto atual, marcado pelo aumento da longevidade no mundo, crescente exigência e expectativas dos cidadãos,

elevados custos com as despesas em saúde e de alguma forma escassez de recursos. Em Portugal, conforme demonstram Carlos Costa e Silvia Lopes [36, 37], nos últimos anos, de entre outros indicadores de resultados, as CPO também têm sido um parâmetro de avaliação de desempenho hospitalar. No entanto, reconhece-se uma grande dificuldade nesta área, uma vez que os registos locais ou internacionais de morbidade de qualidade são poucos e carecem de sistematização na sua codificação. Assim, os únicos meios disponíveis para a comunidade científica e a sociedade em geral avaliar a morbidade pós-operatória associada a procedimentos cirúrgicos específicos são estudos isolados publicados por serviços cirúrgicos específicos, que não são auditados externamente e que também apresentam as suas limitações [38]. Através de uma análise crítica da qualidade da literatura cirúrgica publicada entre 1975 a 2001 sobre o relato das CPO, Martin et al., [39] observaram que apenas 34% dos estudos definiram o termo “complicação”, as definições utilizadas eram várias (ex: para fístula pancreática, foram encontradas 12 definições diferentes) e apenas 20% apresentaram informação sobre a severidade. Estas dificuldades são ainda sentidas nos dias de hoje e dificultam não só a caracterização real do problema, mas também a elaboração e avaliação da eficácia de estratégias perioperatórias para prevenção das CPO e mitigação dos seus efeitos adversos [32]. De sublinhar ainda que, sem uma métrica comum, a utilização dos dados de incidência, severidade e morbilidade resultante das CPO para avaliar e comparar a qualidade dos cuidados prestados estará limitada [40].

Em 1992, Clavien et al., [41] apresentarem uma proposta de classificação das complicações cirúrgicas baseada em princípios gerais e definições, para aplicação no contexto das colecistectomias. A terapia empregue no tratamento das complicações cirúrgicas foi o ponto referencial para a diferenciação dos seus níveis de gravidade. Após 12 anos, Dindo et al., em 2004, apresentaram uma versão aprimorada para classificação das complicações cirúrgicas, baseada na primeira proposta [42]. Desde então, o grupo de Pierre Alain Clavien tem vindo a conduzir uma série de estudos, preconizando novas metodologias para classificar as complicações cirúrgicas, testando a confiabilidade do método e submetendo-o a testes em diversos centros em várias regiões do globo [40, 41, 43, 44]. Existem, no entanto, algumas limitações apontadas, nomeadamente o

facto do percurso pós-operatório ser orientado de acordo com a complicação mais grave, desconsiderando o eventual contributo cumulativo de outras complicações, nomeadamente as de menor severidade, sendo que entre 44% e 51,5% dos doentes que apresentam morbidade nos serviços cirúrgicos apresentam duas ou mais complicações menores [38]. Para superar esta limitação e tentar integrar todas as complicações, foram propostos outros sistemas de classificação, desenvolvidos a partir do sistema de CCD, dos quais se destaca o Comprehensive Complication Index (CCI). Proposto em 2013 por Slankamenac et al [44], este sistema integra todas as complicações e a sua gravidade numa escala linear que varia de 0 (sem complicações) a 100 (morte) [44]. A sua validade externa tem sido estudada [45] e alguns estudos defendem inclusive a sua superioridade, comparativamente ao CCD, em termos de associação com a morbilidade e mortalidade pós-cirúrgica [46-48]. No entanto, o sistema de Clavien-Dindo (CCD) ainda é o sistema mais utilizado para classificar CPO de maneira objetiva e reprodutível, sendo também recomendado por diversas sociedades internacionais de especialidades médicas [49].

1.3.2. Incidência

A incidência global das CPO a 30 dias situa-se entre os 5% e 45% para a cirurgia eletiva [50, 51]. No contexto oncológico, e especificamente no CGI, encontram-se descritas incidências de CPO de aproximadamente 33,5 até 51% após esofagectomia [52, 53], 20 a 40% após gastrectomia [54, 55], 12 a 30% após colectomia (REF), 14 a 27% após cirurgia colorretal e 30 a 60% após pancreatectomia [56]. Estas variações refletem a influência de múltiplos fatores, incluindo as características do doente (ex: idade, reserva fisiológica, tipo e estádio da doença oncológica subjacente, presença concomitante de comorbilidades e fatores de risco), o procedimento cirúrgico [57], o volume de cirurgias realizadas [58] os recursos humanos, técnicos e estruturais disponíveis [59], mas também a variabilidade inerente à utilização de diferentes critérios para a descrição e classificação das CPO [60]. Ao mesmo tempo que são fonte de variabilidade, todas estas áreas correspondem a oportunidades de inovação, que carecem de atenção, na expetativa de melhorar os cuidados de saúde prestados.

Dentro das CPO secundárias à cirurgia ao trato gastrointestinal, as complicações pulmonares, a infeção do local cirúrgico e as deiscências da anastomose são as mais prevalentes bem como as que maior impacto exerce sobre a mortalidade pós-cirúrgica, o tempo de internamento e a necessidade de reoperar [57, 61, 62]. A infeção do local cirúrgico é a complicação mais frequente, sendo um importante motivo de dor e sofrimento para o doente. A nível global, estima-se que a sua incidência seja de 12,3% até aos 30 dias após cirúrgica, com incidências de 9,4%, 14% e 23,2% a serem observadas em países de elevado, médio e baixo índice de desenvolvimento humano, respetivamente [63]. Verificou-se ainda que a maior incidência de infeção do local cirúrgico ocorre após cirurgia considerada contaminada (17,8%, 31,4% e 39,8% para países de elevado, médio e baixo índice de desenvolvimento humano, respetivamente) [63]. Estima-se que 30% das mesmas poderão ser prevenidas com a implementação de medidas pré e intraoperatórias [64]. Depois das complicações relacionadas à infeção do local cirúrgico, as complicações pulmonares pós-operatórias (CPP) são o segundo tipo mais comum, com uma incidência que pode variar de 2 a 40% [65], sendo mais comuns na cirurgia ao abdómen superior [66]. As CPP mais frequentemente descritas em cirurgia abdominal, são: insuficiência respiratória, pneumonia, reintubação traqueal dentro de 48 horas, atelectasia, broncospasmo, exacerbação de doença pulmonar obstrutiva crónica (DPOC), pneumotórax e derrame pleural. Vários estudos sugerem que as CPP são inclusive mais comuns do que as complicações cardíacas [61]. No plano infecioso, alguns autores relatam que a pneumonia hospitalar é considerada a segunda infeção mais frequente entre as infeções hospitalares, chegando a acometer 18 a 68% dos doentes submetidos a cirurgia [67-72]. Além disso, a pneumonia, entre outras CPP como a atelectasia e a ventilação mecânica, ou ainda a transfusão, choque (séptico, hemorrágico ou anafilático) e administração excessiva de líquidos perioperatórios, aumentam significativamente a suscetibilidade à síndrome de distress respiratório agudo (ARDS). Esta síndrome representa a principal causa de insuficiência respiratória no pós-operatório, levando à admissão nos cuidados intensivos, com uma taxa de mortalidade que pode chegar aos 76% [73]. Embora não sendo a área de foco do presente trabalho, gostaríamos de destacar que, durante os últimos anos, participamos em diversos estudos sobre a ARDS nos doentes admitidos em UCI,

nomeadamente na sua caracterização epidemiológica, causas e fatores de agravamento modificáveis, diagnóstico precoce, prognóstico e tratamento [74-81]. O conhecimento acumulado leva-nos a reforçar a importância das estratégias de prevenção, que podem incluir pré-habilitação no período pré-operatório e ventilação não-invasiva no período pós-operatório.

A maioria dos estudos realizados em Portugal sobre CPO sugerem que muitas delas têm sido, de alguma forma, relegadas para segundo plano, do ponto de vista da sua ocorrência e monitorização, e, sem receio de errar é lícito poder afirmar haver em território nacional, ainda pouca evidência científica especialmente em determinadas cirurgias. Estudar as CPO em cirurgia abdominal, particularmente as CPP, conhecer a sua real incidência e os mecanismos envolvidos na sua ocorrência parece-nos muito importante, pois permitirá identificar os fatores de risco predisponentes contribuindo para a sua identificação precoce e para o delineamento de estratégias da sua prevenção.

1.3.3. Mortalidade e morbilidade pós-operatória

A nível global, a mortalidade pós-operatória varia entre 1% a 4% para a cirurgia eletiva [50, 51, 82]. Uma vez mais, a variabilidade é atribuída a múltiplos fatores (abordados na próxima secção) [59], mas sem dúvida que a própria definição de mortalidade pós-operatória (ex: 24h, 7 dias ou 30 dias após) também contribuirá [83]. Se atendermos à quantidade de procedimentos realizados em todo o mundo, a taxa de mortalidade pós-operatória traduz-se em aproximadamente 4,2 milhões de mortes, sendo que metade dessas mortes ocorrem em países de baixa-média renda. Estes números correspondem a 7,7% de todas as mortes em todo o mundo, colocando a mortalidade pós-operatória como a terceira principal causa de morte, logo atrás da doença cardíaca isquémica e do acidente vascular cerebral [84]. Já a incidência de mortalidade por CPO (failure to rescue) varia de 8.0 a 16.9% [85]. Curiosamente, verificou-se que nos países de menor renda, a mortalidade por CPO após cirurgia eletiva geral é duas vezes superior à média global, apesar dos doentes serem mais jovens, terem um menor perfil de risco menor e uma taxa de complicações mais baixa [86]. Para as CPP, tema de estudo do presente trabalho, estima-se uma mortalidade de 14-30% aos 30 dias

após a cirurgia em doentes que desenvolveram CPP, em comparação com 0,2-3% dos doentes sem CPP [87].

A ocorrência de complicações no período pós-operatório limita de forma marcada o prognóstico do doente oncológico submetido a cirurgia. Se por um lado poderá debilitar o doente, atrasar a quimioterapia e reduzir os seus potenciais efeitos benéficos, por outro poderá prolongar o período de internamento, aumentar o risco de readmissão hospitalar e a necessidade de cuidados continuados, aumentar os custos, diminuir a qualidade de vida e precipitar a morte prematura [54, 59, 88-91]. De notar ainda que a ocorrência de complicações até 30 dias pós-cirurgia major mostrou ser um determinante da sobrevida a longo prazo [92-94], com impacto mais importante do que o risco pré-operatório ou do que fatores intraoperatórios [87, 95-97]. Existe também evidência de que as CPO podem induzir um efeito supressor de longa duração no sistema imunológico dos doentes, tornando-os mais suscetíveis a recorrência da neoplasia [93, 98, 99]. Foi também demonstrada uma associação entre CPO (major e minor) perturbação do bem-estar psicossocial do doente, nomeadamente com níveis elevados de stress e depressão, até 12 meses após a cirurgia [100]. Considerando a perspetiva de incremento do volume global de cirurgias, a transição demográfica populacional e as melhorias no acesso a tratamento cirúrgico nos países em crescimento, antevê-se que estes números possam também aumentar nos próximos anos.

De destacar ainda que para a maioria dos doentes, os riscos apresentados pela cirurgia são baixos. De facto, oculto dentro da população cirúrgica, encontra-se um subgrupo de doentes, que apesar de representaram apenas 15-20% desta população, contribuem com cerca de 80-90% para a mortalidade pós-operatória [59, 89, 101]. Fazem parte deste grupo os doentes geriátricos com necessidade de cirurgia major ou de urgência, nos quais o receio de aumentar a morbilidade e mortalidade pós-operatória determina que por vezes os procedimentos cirúrgicos com intenção curativa ou paliativa sejam preteridos ou subotimizados em doentes que beneficiaram desses cuidados [102]. No entanto, dentro deste grupo de doentes existe grande heterogeneidade como sugere a observação de que apenas uma minoria de doentes com idade superior a 80 anos morre ou sofre CPO até 30 dias no contexto de cirurgia não-cardíaca major [103].

Consequentemente, tem havido um enorme interesse no esclarecimento dos múltiplos fatores que poderão contribuir para essa variabilidade, com o intuito de estratificar o risco e aumentar a acurácia da identificação do doente de risco, podendo assim auxiliar verdadeiramente na decisão sobre o plano terapêutico.

Em suma, o produto final das CPO é uma maior morbimortalidade e um acréscimo no consumo de recursos, que afeta a efetividade dos cuidados e a sua eficiência, com implicações para os doentes, hospitais e comunidade [104-109]. Este facto demonstra a grande importância clínica das complicações pós-operatórias, ficando subjacente a necessidade de uma análise criteriosa das mesmas, dos fatores de risco a elas associadas e de como as prevenir [87, 110-112].

1.3.4. Fatores de predisposição para a morbilidade e mortalidade pós-operatória

O conhecimento dos fatores associados à morbilidade e mortalidade pós-operatória permitirão uma melhor tomada de decisão clínica, não apenas para agir preventivamente e corrigir fatores modificáveis, mas também para operar no momento certo, otimizar os resultados cirúrgicos e gerir recursos. Dentro desses fatores encontram-se variáveis relacionadas com o próprio indivíduo (ex: idade, características anatómicas, reserva fisiológica, presença concomitante de comorbilidades, fatores de risco e síndromes geriátricos) [95, 113-118], com a doença (ex: localização e estádio), com a cirurgia (ex: conhecimento e capacidades técnicas, experiência da equipa cirúrgica, volume de cirurgias realizadas, tipo e complexidade cirúrgica) [57, 58, 119] e com o sistema de saúde (ex: recursos técnicos e estruturais disponíveis) [120]. Em seguida, faremos uma breve revisão sobre aqueles que julgamos serem mais pertinentes para o âmbito do presente trabalho.

Os doentes idosos são reportados sistematicamente como os mais afetados, por exemplo, pelas pneumonias [121, 122]. O envelhecimento fisiológico é caracterizado por redução da complacência da parede torácica e pelo aumento da complacência pulmonar e resistência das vias aéreas, o que aumenta o esforço ventilatório. A diminuição da força dos músculos respiratórios e dos

reflexos da tosse e deglutição, bem como a diminuição do número e funcionalidade ciliar diminuem a clearance de secreções. Também ocorre uma diminuição da pressão parcial de oxigénio e um aumento do espaço morto o que provoca uma diminuição da relação ventilação-perfusão pulmonar [123, 124]. Estes fatores, associados a algumas condições do período pós-operatório como a imobilidade e o uso de narcóticos, de modo geral, culminam em uma elevada probabilidade de ocorrerem atelectasias e aspiração pulmonar com o desenvolvimento de pneumonia [125-128]. No entanto, como referido anteriormente, apesar de se esperar um aumento da incidência de complicações pós-operatórias com o aumento da idade, nem sempre isso é observado [103]. As alterações estruturais e funcionais dos sistemas fisiológicos ocorrem a velocidades distintas entre indivíduos com a mesma idade, motivo pelo qual o impacto da idade cronológica deve ser sempre ponderado juntamente com outras características do doente. Alias, mais do que a idade cronológica, tem crescido o interesse sobre a idade biológica na população cirúrgica, característica esta que reflete as alterações da reserva fisiológica. Fragilidade é um termo utilizado para definir esse estado de diminuição da reserva funcional e de maior vulnerabilidade a agentes agressores como a cirurgia [129-131]. Estima-se que mais de 50% dos doentes geriátricos oncológicos sejam classificados como frágeis ou pré-frágeis [132]. Apesar de não haver consenso sobre a ferramenta mais adequada para avaliar a fragilidade [133], a literatura é unânime em considerar que os doentes com maior índice de fragilidade pré-operatória, quando submetidos a cirurgia, apresentam maior risco de complicações [129, 134, 135], incluindo pulmonares (ex: reintubação, pneumonia, ventilação prolongada) [136], maior declínio funcional e perda de qualidade de vida [135], e maior risco de mortalidade a 30 dias [129] ou a 1 ano [130]. De destacar que a fragilidade é reversível, com evidência preliminar a indicar que a otimização pré-cirúrgica de doentes oncológicos frágeis, através de programas de pré-habilitação, diminuiu a incidência de complicações severas e reduziu a mortalidade a 30 dias [137].

É geralmente estabelecida uma associação importante entre o tabagismo e as complicações pulmonares pós-operatórias, acreditando alguns autores que a relação do tabagismo com as CPP possa ser indireta, uma vez que os sintomas

respiratórios são três a quatro vezes maiores nos fumantes que nos não fumantes [138-140]. Os fumadores apresentam normalmente alterações fisiológicas que podem alterar as respostas a procedimentos cirúrgicos, contribuindo para o aumento da morbilidade pós-operatória pelo risco elevado de desenvolvimento de complicações respiratórias, cardiovasculares e de cicatrização. Uma das principais alterações implicadas no tabagismo é a danificação dos cílios da mucosa traqueobrônquica e o aumento da produção de muco com consistência elevada, além de aumentada suscetibilidade ao colapso alveolar, levando a maior probabilidade de infeção nas vias aéreas inferiores e a ventilação mecânica prolongada [141]. Assim sendo, a abstinência do cigarro no período pré-operatório, principalmente por mais de oito semanas, pode reduzir a frequência e a intensidade dos sintomas e levar a uma redução na incidência de CPP (redução até 47%) [142-144].

Por outro lado, a presença concomitante de comorbilidades como a doença pulmonar obstrutiva crónica (DPOC), hipertensão arterial sistémica, cardiopatia e diabetes mellitus já foram previamente descritas em associação com maior risco para CPP [145, 146]. Especificamente sobre a diabetes mellitus, os doentes diabéticos apresentam um risco quase cinco vezes maior de complicações após a cirurgia [147], realçando a importância do controlo metabólico prévio ao procedimento cirúrgico como um fator importante na prevenção de complicações. Hiperglicemia ou valores elevados de hemoglobina glicosilada em doentes com cancro gastrointestinal encontram-se associados a risco aumentado de desenvolvimento de várias complicações pós-operatórias, como as infeções (ex: local cirúrgico) e as respiratórias (ex: pneumonia) [148, 149]. O controle glicémico perioperatório parece reduzir não apenas a taxa de incidência de complicações pós-operatórias [150, 151], mas também melhorar o prognóstico a longo prazo [152, 153]. Já sobre a doença pulmonar prévia, esta também tem geralmente uma associação significativa com as CPP, sendo que a presença de DPOC é um fator de risco importante para o desenvolvimento de CPP, com um risco maior do que 18% em alguns estudos, que varia com a gravidade da doença [154-158]. Embora isso seja verdade, quando tratados e controlados previamente ao procedimento cirúrgico, os doentes com DPOC apresentam a mesma incidência de CPP que os indivíduos sãos [159, 160].

Os extremos do estado nutricional, desnutrição e obesidade, também têm influência sobre o risco de desenvolvimento de CPP. A desnutrição pode estar presente em 80% dos doentes com cancro gastrointestinal em estágio avançado [161-164], associando-se a maiores riscos de infeção pós-operatória e a um aumento na morbimortalidade [124-126]. Em desnutridos, a albumina sérica baixa é um risco estabelecido para o desenvolvimento de CPP porque se associa a alteração da dinâmica pulmonar e funcionamento de músculos respiratórios, estando relacionada a maiores taxas de pneumonia [165, 166]. O suporte nutricional parece reduzir significativamente a morbilidade [167, 168]. Por outro lado, doentes obesos apresentam alterações fisiológicas importantes, como a diminuição da relação ventilação-perfusão devido à hipoventilação e à elevada perfusão tecidual. Apresentam também diminuição da complacência pulmonar e do movimento da caixa torácica secundariamente ao acúmulo de tecido adiposo na parede torácica e na cavidade abdominal, dificultando a mobilidade diafragmática. Além disso, doentes obesos são mais dificilmente mobilizados durante o pós-operatório, o que implica maior risco de trombose venosa profunda e consequentemente tromboembolismo pulmonar [169, 170]. Já no outro extremo, temos os doentes com doença neoplásica maligna grave, frequentemente com síndrome de anorexia-caquexia (SAC), caracterizando-se essa síndrome por um intenso consumo, com consequente perda involuntária de peso, desnutrição, alterações fisiológicas, metabólicas e imunológicas [161-164].

Destacam-se ainda a influência de fatores operatórios. A anestesia geral pode associar-se ao desenvolvimento de complicações respiratórias, dado que a intubação endotraqueal e o relaxamento muscular a ela associada, pode provocar aspiração brônquica [171, 172]. Por outro lado, a assistência ventilatória ao deprimir o sistema nervoso central reduz o reflexo da tosse o que aumenta o risco de pneumonias [173]. Nos procedimentos cirúrgicos e suas possíveis complicações, um dos pontos controversos é a possibilidade de diferenças significativas entre as complicações no caso de cirurgias eletivas e de urgência/emergência. Alguns estudos demonstram a existência destas diferenças na incidência de complicações respiratórias, pois os doentes submetidos aos procedimentos eletivos encontraram-se mais bem preparados do ponto de vista clínico [95, 174]. Também as incisões no abdómen superior e

no tórax apresentaram maior incidência de complicações, o que se deve ao fato de estas vias de acesso reduzirem em 50 a 60% a capacidade vital, e em 30% a capacidade funcional residual, por disfunção do diafragma. De igual modo, a inibição reflexa do nervo frénico pela manipulação visceral, a dor pós-operatória, o colapso alveolar normalmente presentes nestes tipos de incisões explicam a maior incidência de CPO, pulmonares em especial [175-177]. A duração da cirurgia configura-se como um fator de risco igualmente importante, referindo a literatura que um tempo de cirurgia entre 210 e 360 minutos determina uma maior incidência de CPP, sendo que quanto mais prolongado o procedimento, maior é a possibilidade de desenvolvimento de CPP. Tal deve-se à associação de vários fatores de risco, como a exposição prolongada à anestesia geral e seus efeitos deletérios sobre a função respiratória, a incisão no abdómen superior ou tórax, assim como procedimentos invasivos, como o uso de drenos, de sondas e a manipulação dos doentes que necessitam de cuidados intensivos no período pós-operatório [178]. O grau de contaminação também é normalmente associado a maior ocorrência de CPP em vários estudos, e os doentes submetidos às cirurgias infetadas têm um maior risco de desenvolver complicações dessa natureza [179]. As reintervenções cirúrgicas constituem também fatores de risco, ao condicionarem a reexposição dos doentes ao jejum prolongado antes e depois da cirurgia, stress cirúrgico, anestesia (principalmente a geral), queda da imunidade, repouso prolongado, dor, procedimentos invasivos e hospitalização prolongada, propiciando tudo isso ao desenvolvimento de CPP [180].

1.4 Instrumentos de risco perioperatório e seus resultados

É inevitável que a morbilidade e a mortalidade perioperatória sejam influenciadas pelo estado de saúde do doente, a complexidade dos procedimentos cirúrgicos e o sucesso do manejo anestésico. Os preditores de risco cirúrgico e os sistemas de pontuação co-relacionados, procuram incorporar essas características, com o intuito de fornecer uma estimativa confiável e objetiva do prognóstico da doença, a probabilidade de eventos adversos e sua evolução. A procura de uma metodologia de identificação de doentes com risco elevado de desenvolverem

complicações após um ato cirúrgico, reprodutível e fiável é uma preocupação antiga. A identificação de variáveis informativas, a sua avaliação e classificação, o momento em que se realiza, a recolha dos dados, a validade e aplicabilidade em populações distintas, o peso de cada variável são alguns dos desafios e dificuldades quando se pretende criar um instrumento que permita estimar a probabilidade da ocorrência de um evento nefasto.

O primeiro instrumento de avaliação de risco cirúrgico publicado na literatura data da década de 1940 [181]. Este instrumento foi desenvolvido por Meyer Saklad, que tinha como objectivo uma avaliação estatística e foi denominado *Operative Risk*. Este, avaliava o estado físico do doente e graduava-o em 6 classes nomeadamente: I - sem patologia orgânica conhecida, II - patologia moderada mas definitiva, III - patologia sistémica severa, IV - patologia extrema sistémica, V - cirurgia de emergência envolvendo doentes da classe 1 e 2 e VI - cirurgia de emergência envolvendo doentes da classe 3 e 4. Esta classificação foi revista em 1963 sendo o número de classes reduzida de sete para cinco e a operação de emergência anotada com a colocação de um “E”. Posteriormente foi adotada pela *American Society of Anesthesiologist* e é conhecida actualmente como a classificação ASA [182].

Posteriormente foram desenvolvidos outros instrumentos preditivos do risco cirúrgico. O índice de Goldman foi nesse contexto utilizado com sucesso [183]. Copeland e colaboradores desenvolveram um instrumento que incluiu, também, a complexidade cirúrgica como variável e é conhecido como POSSUM score [184]. Mais tarde Klein desenvolveu um instrumento de avaliação intra-operatória e evolução no pós-operatório denominado *Intraoperative Therapeutic Intervention Score* [185]. Este índice de intervenção terapêutica intraoperatória (I-TIS) foi desenvolvido usando um esquema de pontuação semelhante ao utilizado pelo sistema de intervenção terapêutica conhecido como TISS e introduzido por Keene e Cullen [186].

1.4.1. Instrumentos de previsão de risco cardiovascular

Vários instrumentos avaliação de risco cardiovascular perioperatório foram construídos, nomeadamente: *ASA-PS* (American Society of Anesthesiologists Physical Status Classification), *índice de Goldman*, *índice de Detsky*, *índice de Larsen, EMAPO* (Estudo Multicêntrico de Avaliação Perioperatória), *ACS NSQIP* (American College of Surgeons National Surgical Quality Improvement Program, ACC/AHA (American College of Cardiology/American Heart Association) e o índice cardíaco revisto por Lee [187, 188].

O índice de risco cardíaco descrito por Goldman et al., em 1977, foi o primeiro modelo multifatorial específico para complicações cardíacas perioperatórias [183]. Esse índice contempla variáveis referentes à avaliação clínica, eletrocardiograma e o tipo de cirurgia (intra-abdominal, intratorácica, aórtica ou de emergência), conferindo pontuações com intuito de estratificar o doente nas classes I a IV quanto ao risco de apresentar complicações cardiovasculares ou evoluir para óbito.

1.4.2. Instrumentos de previsão de risco respiratório

No que concerne a avaliação do risco de CPP, em dois importantes estudos europeus, um utilizando o ARISCAT *risk score* e a Avaliação Prospectiva de um score de Risco para CPP na Europa (PERISCOPE), são referenciadas taxas de incidência de 5% e 7,9% em doentes submetidos a cirurgia não cardíaca, respectivamente [189, 190]. Porém, vários estudos sugerem que os instrumentos preditivos de avaliação de CPP podem não ser aplicáveis a todas as populações de doentes [127, 191].

Apesar desta limitação, o score ARISCAT conseguiu identificar doentes de baixo risco, risco intermédio e alto risco com alguma fiabilidade [192, 193]. Assim, tornou-se rotineira a utilização do ARISCAT *risk score* na avaliação pré-operatória no sentido de ajudar a identificar doentes com maior risco de desenvolver CPP [158, 189, 190, 194].

1.4.3. Instrumentos de previsão da morbilidade e mortalidade

Em 1991, Copeland e colegas desenvolveram o Physiological and Operation Severity Score for the EnUmeration of Mortality and Morbidity (POSSUM) para ajustar o risco às intervenções cirúrgicas, e cujo objectivo final era realizar auditorias e comparar resultados em distintos centros [184]. Este instrumento revelou ter maior acuidade na previsão da morbilidade do que a mortalidade [192]. A versão modificada denominada P (Portsmouth) - POSSUM score, construída mais tarde, prevê o risco de complicações e mortalidade nos 30 dias após a cirurgia [127, 192, 193] e tem sido amplamente recomendado para previsão da mortalidade [192, 195-198].

Em vários estudos, o P-POSSUM score foi capaz de prever a morbilidade e a mortalidade, no entanto a precisão em doentes com baixo risco de complicações e mortalidade é baixa, uma vez que superestima o risco nesse grupo de doentes, tornando a ferramenta defeituosa e inadequada para avaliar esse perfil desses doentes. Quanto mais 'arriscado' for o procedimento cirúrgico, mais preciso é o risco previsto calculado [193, 199-201].

Em outros estudos o score P-POSSUM foi capaz de prever a morbilidade e mortalidade de maneira confiável quando realizada por categorias especificas de doentes [59, 87, 202-205].

O *ACS NSQIP* (American College of Surgeons National Surgical Quality Improvement Program) desenvolveu um instrumento que estima o risco de complicações pós-operatórias. O risco é estimado com base nas informações que o doente dá ao profissional de saúde sobre o seu histórico de saúde. As estimativas são calculadas a partir de dados de um grande número de doentes que tiveram um procedimento cirúrgico semelhante. Vários investigadores têm criticado a acuidade deste instrumento em determinados procedimentos cirúrgicos. Por exemplo, um estudo sobre cirurgia colorretal descobriu que a ferramenta "subestimou a infecção do local cirúrgico e as taxas globais de complicações". Um problema importante é que os autores não revelam o algoritmo utilizado o que limita a sua compreensão. A acuidade do instrumento foi avaliada num estudo realizado em 2017 em que se conclui que as falhas observadas não desqualificam a ferramenta como precisa e apropriada para o

propósito pretendido que é o de oferecer uma calculadora de risco para uso geral, aplicável em muitos domínios cirúrgicos, usando facilmente informações preditivas e geralmente disponíveis. Este instrumento está disponível *online,* é actualizado regularmente e é utilizado com frequência pela comunidade cirúrgica [206].

1.4.4. Estudos comparativos entre os instrumentos de previsão de risco

Pese embora a utilização dos vários instrumentos seja referenciada na maioria dos trabalhos, poucos são os que os comparam entre si [207, 208], e não existe até ao momento um que se destaque. As comparações realizadas têm encontrado diferenças importantes, porém o tamanho das amostras destes estudos é reduzido [209, 210].

Em 1997, Prause et al. [211] comparou os índices de Goldman e ASA numa amostra de 16.227 doentes submetidos a cirurgia não cardíaca. Segundo os resultados, ambos os instrumentos tiveram um alto grau de correlação (teste de correlação de Spearman's: r=0,92). Todas as categorias dos dois índices apresentaram significância estatística com a mortalidade. O score ASA $\leq$ 3 apresentou uma significância um pouco mais elevada do que o score de Goldman. O uso dos dois instrumentos de forma combinada aumentou a acurácia na predição da mortalidade perioperatória, sendo uma estratégia que se revelou útil [212].

Outros estudos compararam as pontuações das variáveis que espelham a gravidade fisiológica ou a operatória. O desenvolvimento de modelos de mortalidade e morbidade pós-operatória para populações específicas de doentes, ou de procedimentos em cirurgia oncológica tem sido outra metodologia utiizada na tentativa de se obter maior acuidade [197, 213-215].

Em conclusão, podemos afirmar que na prática clinica diária, a previsão da morbilidade e mortalidade pós-operatória pode ser feita utilizando vários instrumentos de risco cirúrgico.

As limitações encontradas nos diferentes estudos analisados demonstram que a investigação, nesta área do saber, não está concluída. Há necessidade de mais

estudos fundamentalmente prospectivos sobre a temática das CPO em cirurgia oncológica digestiva, de forma a identificar os doentes de maior risco, expondo-os a um programa de pre-habilitação pré-operatória no sentido de melhorar a reserva fisiológica. No futuro a aplicação da inteligência artificial neste contexto poderá melhorar a performance da avaliação do risco cirúrgico.

1.5 Prevenção da morbilidade e mortalidade pós-cirúrgica

A prevenção ou mitigação da morbilidade e mortalidade pós-cirúrgica deve englobar a implementação de um conjunto de medidas ou intervenções perioperatórias, que têm início com a identificação dos doentes de alto risco. A identificação precoce destes doentes facilita a tomada de decisões sobre o tratamento cirúrgico, permite orientar a individualização dos cuidados perioperatórios [181, 182] e antecipar e planear pós-operatórios (ex: necessidade de cuidados intensivos) [183, 184]. Como referenciado anteriormente, exsitem na atualidade várias escalas de avaliação do risco de morbilidade e mortalidade pós-operatória com objetivo de auxiliar na seleção dos doentes elegíveis a cirurgia. Entre os mais utilizados, destacam-se instrumentos de previsão de risco perioperatório como o American Society of Anesthesiologists (ASA) physical status classification system (ASA PS score), o Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality (P-Possum score), o American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Surgical Risk Calculator (SRC), o Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) [185-191].

Apesar da sua utilização generalizada para predizer a morbilidade e mortalidade na população cirúrgica, estes instrumentos apresentam importantes limitações e nem sempre a sua performance preditiva é adequada, havendo espaço para melhorias. Desde logo, porque a maioria foi desenvolvida há várias décadas, com métodos estatísticos pouco sofisticados, com base em variáveis/informações limitadas (em quantidade e qualidade) e tendo como referência um perfil de doentes, técnicas cirúrgicas e anestésicas, meios hospitalares e regimes terapêuticos que não serão certamente representativas

dos dias de hoje [192]. De notar também que, para muitos destes instrumentos, a validade externa ou utilidade em populações cirúrgicas específicas, como a concológica, permanece por esclarecer [193], idealmente através de estudos prospetivos bem desenhados. De facto, muitos dos estudos que avaliaram a utilidade destes instrumentos na população oncológica são retrospetivos, logo sujeitos ao viés na recolha da informação (inconsistente e/ou incompleta) e utilizam coortes de pequena dimensão [194, 195]. Adicionalmente, muitos destes modelos requerem a introdução de informação intraoperatória, o que limita a sua utilização pré-operatória. Todas estas limitações se tornam evidentes, por exemplo, se verificarmos a abundância de estudos que, com cada vez maior frequência, observam um desajuste importante entre aquilo que foi predito e aquilo que foi observado [192, 195, 196] ou ainda a falta de concordância entre diferentes instrumentos [197-199]. Sobre este especto, destaca-se o ACS NSQIP, considerado um dos instrumentos mais robustos [119], o qual é constantemente atualizado à medida que o conhecimento na área evolui, com os promotores deste instrumento a estimularem a comunidade cientifica e médica à identificação de variáveis críticas específicas (do procedimento cirúrgico ou do doente) que possam ser utilizadas para melhorar cada vez mais a performance do modelo. Por exemplo, recentemente, o modelo foi otimizado para predizer outcomes geriátricos (úlceras de pressão, delírio, necessidade de auxílio à mobilidade e declínio funcional) [200]. Ainda assim, a sua validade externa não tem sido confirmada em vários estudos [201-204], particularmente no contexto das neoplasias do trato gastrointestinal.

Portanto, apesar do seu potencial, é determinante analisar e comparar os scores preditivos de risco perioperatórios correntemente usados, comparando a sua acurácia (isolada ou combinada) enquanto instrumentos específicos de avaliação de risco, de previsão de morbimortalidade, e não menos importante é identificar as variáveis mais informativas de risco cirúrgico de cada um dos diferentes scores preditivos (e/ou incorporar outras), com o objetivo de otimizar a sua eficácia. Sobre este especto, gostaríamos de destacar o nosso contributo recente através da análise retrospetiva de uma coorte de 128 doentes com neoplasia da cabeça e pescoço admitidos na unidade de cuidados intermédios após a cirurgia [205]. Avaliamos e comparamos a performance dos instrumentos

ASA PS score, P-POSSUM, ACS-NSQIP e ARISCAT para predizer as complicações e mortalidade pós-cirúrgica e verificamos que, individualmente, o valor destes instrumentos é limitado. Contudo, quando combinamos as variáveis do ACS-NSQIP e ARISCAT, melhoramos a previsão do risco de complicações graves [205].

É igualmente importante aproveitar a tecnologia mais avançada que dispomos hoje para desenvolver novos modelos preditivos, que sejam o mais abrangentes possível, que considerem todos os fatores de risco possíveis, os avalie quantitativamente, considere todas as interações possíveis entre eles, seja adequado para qualquer paciente e condição cirúrgica e que seja capaz de integrar e aprender continuamente com toda a informação que vai sendo gerada ao longo do percurso do doente. No momento poderá parecer uma utopia, mas com o advento da inteligência artificial, big data e desenvolvimento de áreas como o machine learning, natural language processing poderão vir a facilitar a missão [206, 207]. Além da otimização dos instrumentos de identificação dos doentes de risco, é fundamental desenvolver estratégias capazes de modular esse mesmo risco e, consequentemente, mitigar a morbimortalidade pós-cirúrgica. Enquanto os doentes considerados de baixo risco poderão avançar para a cirurgia sem necessidade de grandes preparações, intervenções ou atrasos, os doentes de alto risco deverão ser alvo de intervenções perioperatórias individualizas, que sejam capazes não só de prevenir, mas também de detetar (precocemente) e tratar as complicações pós-operatórias. No período pré-operatório, a pré-habilitação é a maneira mais eficaz de otimizar o doente de risco e prevenir a morbimortalidade pós-operatória. Pré-habilitação é um termo abrangente que inclui qualquer intervenção com a finalidade de aumentar a reserva fisiológica e tolerância ao stress imposto por uma agressão aguda como o tratamento cirúrgico. Compreende a combinação de intervenções como exercício físico, cuidados nutricionais e/ou psicológicos, além da otimização médica (ex: controlo de fatores de risco, comorbilidades e medicação) [208]. A evidência atual corrobora a sua segurança e eficácia na mitigação das CPO na cirurgia abdominal e torácica geral, mas também em doentes com neoplasia do esófago, colorretal ou do pulmão [209-211], incluindo em doentes de alto risco [181], onde se observou uma redução das complicações

em cerca de 50%. Apesar disto, a pré-habilitação é ainda claramente subutilizada.

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Capítulo II - OBJETIVOS

A investigação oncológica, básica, translacional, clínica e epidemiológica tem permitido enormes progressos na prevenção, diagnóstico e tratamento do cancro, sendo muito importante o desenvolvimento de projetos inovadores e com aplicação clínica, os quais devem ter uma dimensão fundamental na prossecução da melhoria constante dos cuidados prestados aos doentes oncológicos, no sentido de oferecer diariamente os melhores métodos de prevenção e tratamento desta doença. O presente trabalho, focado na identificação e prevenção das CPO, pretende ser um humilde contributo. Como observado na nossa breve revisão da literatura, as CPO têm vindo a ocupar um lugar de destaque na literatura científica. Sabemos que representa uma questão muito importante de grande impacto mundial e nacional, com um amplo espectro de gravidade e que por menor que seja o procedimento cirúrgico, o seu risco de desenvolvimento estará sempre presente. Observam-se múltiplos esforços no sentido de as compreender, prever e evitar. Em Portugal, esta questão constitui ainda um assunto pouco caracterizado, sendo a incidência das CPO em cirurgia oncológica digestiva praticamente desconhecida. Os poucos estudos existentes, revelam do nosso ponto de vista algumas fragilidades, pese embora em termos de conteúdo evidenciem conceitos e informações importantes. Enquanto complicação pós-operatória frequente em cirurgia oncológica digestiva, conhecer a prevalência das complicações respiratórias em particular pode revelar-se de grande utilidade, ao permitir-nos intervir precocemente através de intervenções programadas (pré-habilitação), mitigando o risco de complicações pós-operatórias e em consequência melhorar a sobrevivência. Assim, estabelecemos os seguintes objetivos:

1) Comparar a precisão de ferramentas de avaliação de risco cirúrgico na predição de complicações pós-operatórias em doentes do foro de oncologia digestiva e propor um novo instrumento de previsão de risco cirúrgico mais proficiente e adaptado à nossa realidade.

2) Caracterizar os fatores de risco perioperatórios para as complicações pulmonares de doentes submetidos a cirurgia abdominal e avaliar a sua associação com a morbilidade e mortalidade pós-operatória.

3) Elaborar uma proposta de mitigação do risco de complicações pós-operatórias através de um programa de pré-habilitação.

Capítulo III - RESULTADOS

Os estudos realizados para responder às questões em estudo constituem este capítulo. Os dados obtidos estão condensados sob a forma de artigos científicos. São apresentadas as cópias integrais dos estudos após autorização para poderem integrar o corpo desta tese.

3.1 Desenvolvimento de um instrumento de avaliação do risco cirúrgico prévio à admissão à unidade cuidados intermédios de cirurgia em doentes com cancro digestivo

A cirurgia do cancro gastrointestinal continua a associar-se uma taxa importante de complicações pós-operatórias e mortalidade em doentes de alto risco. É crucial identificar esses doentes. O nosso estudo teve como objetivo avaliar a precisão de ferramentas de avaliação de risco cirúrgico na predição de complicações pós-operatórias, identificando as variáveis mais informativas e combinando-as, caso não se revelassem úteis, num modelo de previsão de risco cirúrgico mais proficiente e adaptado à nossa realidade.

Metodologia:
Foi realizado um estudo de coorte prospetivo de 341 doentes submetidos a cirurgia oncológica digestiva e admitidos na unidade de cuidados intermédios do Instituto Português de Oncologia do Porto, de janeiro de 2016 a abril de 2018. Foram recolhidos os dados demográficos e clínicos, que incluíram o género, idade, data de diagnóstico, tipo de admissão (urgência ou eletiva) e tipo de cirurgia. Analisamos e comparamos o risco cirúrgico obtido através de um conjunto de instrumentos de avaliação do risco cirúrgico nomeadamente o P-POSSUM Score, ACS NSQIP Surgical Risk Calculator, ASA e ARISCAT Risk Score e as complicações pós-operatórias de acordo com a classificação

proposta por Clavien e Dindo. De acordo com cada sistema de pontuação de risco, estudamos as complicações pós-operatórias esperadas e observadas.

Resultados:

Os nossos resultados revelaram que a precisão e a concordância dessas ferramentas é limitada. Assim, com base nas variáveis mais informativas dessas ferramentas, desenvolvemos um novo modelo de predição de risco cirúrgico, o MyIPOrisk-score, que demonstrou ter maior capacidade de discriminação do que o obtido com cada instrumento previamente utilizado (AUC = 0,808; IC95%: 0,755-0,862).

Conclusão:

Demonstramos a viabilidade e a utilidade do MyIPOrisk-score para a avaliação de doentes submetidos a cirurgia digestiva oncológica. No entanto, será necessária a realização de um estudo prospetivo multicêntrico para validar a performance preditiva deste instrumento de avaliação do risco.

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Development of a preoperative risk score on admission in surgical intermediate care unit in gastrointestinal cancer surgery

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Abstract

Background: Gastrointestinal cancer surgery continues to be a significant cause of postoperative complications and mortality in high-risk patients. It is crucial to identify these patients. Our study aimed to evaluate the accuracy of specific perioperative risk assessment tools to predict postoperative complications, identifying the most informative variables and combining them to test their prediction ability as a new score.

Methods: A prospective cohort study of digestive cancer surgical patients admitted to the surgical intermediate care unit of the Portuguese Oncology Institute of Porto, Portugal was conducted during the period January 2016 to April 2018. Demographic and medical information including sex, age, date from hospital admission, diagnosis, emergency or elective admission, and type of surgery, were collected. We analyzed and compared a set of measurements of surgical risk using the risk assessment instruments P-POSSUM Scoring, ACS NSQIP Surgical Risk Calculator, and ARISCAT Risk Score according to the outcomes classified by the Clavien-Dindo score. According to each risk score system, we studied the expected and observed post-operative complications. We performed a multivariable regression model retaining only the significant variables of these tools (age, gender, physiological P-Possum, and ACS NSQIP serious complication rate) and created a new score (*MyIPOrisk-score*). The predictive ability of each continuous score and the final panel obtained was evaluated using ROC curves and estimating the area under the curve (AUC).

Results: We studied 341 patients. Our results showed that the predictive accuracy and agreement of P-POSSUM Scoring, ACS NSQIP Surgical Risk Calculator, and ARISCAT Risk Score were limited. The *MyIPOrisk-score*, shows to have greater discrimination ability than the one obtained with the other risk tools when evaluated individually (AUC = 0.808; 95% CI: 0.755–0.862). The expected and observed complication rates were similar to the new risk tool as opposed to the other risk calculators.

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Conclusions: The feasibility and usefulness of the *MyIPOrisk-score* have been demonstrated for the evaluation of patients undergoing digestive oncologic surgery. However, it requires further testing through a multicenter prospective study to validate the predictive accuracy of the proposed risk score.

Keywords: Oncological digestive surgeries, Postoperative complications, Preoperative risk scoring, Prediction of mortality

Introduction

Population-based cancer registries worldwide show an increased incidence of gastrointestinal (GI) cancer (Ferlay et al., 2019; Global Burden of Disease Cancer Collaboration, 2017; González & Agudo, 2016). GI cancer includes malignant neoplasms of the esophagus, gallbladder and biliary tract, liver, pancreas, stomach, small intestine, bowel (large intestine or colon and rectum), and anus. Treatment of these tumors mostly involves surgery. Despite the improvements in anesthesia and surgical techniques, GI cancer surgery (GICS) continues to be a major cause of morbidity and mortality (Jhanji et al., 2008; Weiser et al., 2008), contributing to postoperative complications (POC), which in high-risk patients, may be associated with mortality of up to 80% (Mazo et al., 2014; Fernandez-Bustamante et al., 2016). The identification of high-risk patients in the preoperative phase is of crucial importance as it will offer an opportunity to optimize the patient's status with interventions that contribute to recovery, such as prehabilitation (West et al., 2017).

The American Society of Anesthesiologists Physical Status classification system (ASA PS), P-Possum Score, American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), and ARISCAT Risk predictor score for postoperative pulmonary complications are some of the most commonly used perioperative morbidity and mortality risk prediction tools (Hackett et al., 2015; Miskovic & Lumb, 2017; Lubitz et al., 2017; Whiteley et al., 1996). The few prospective studies comparing the accuracy of perioperative risk scoring in GICS and their predictive capacity for mortality and POC provide divergent results, pointing to some limitations in predicting POC. These facts suggest that this area of knowledge is still under-researched (Carvalho-e-Carvalho et al., 2018). Moreover, the lack of consensus on how to define and grade postoperative adverse events has dramatically hampered the evaluation of surgical procedures. To solve this, Clavien-Dindo Classification revealed as an objective and reproducible manner to rank POC complications (Dindo & Clavien, 2004; Chereshneva et al., 2016). Using the classification of surgical complications according to the Clavien-Dindo score, as the outcome, we performed the analysis and comparison of a set of measurements of surgical risk, namely the P-POSSUM Scoring, ACS NSQIP Surgical Risk Calculator, and the ARISCAT Risk Score. The objective was to evaluate their accuracy as perioperative risk assessment instruments in the prediction of postoperative morbidity in GI cancer patients admitted in Surgical Intermediate Care Unit (SICU). The most informative variables from each risk instrument were identified.

Materials and methods

Study design and patient population

A cohort study of GI cancer patients admitted to the surgical intermediate care unit (SICU) of the Portuguese Oncology Institute of Porto, Portugal (IPO-Porto) between January 2016 and April 2018 was conducted retrospectively. Throughout this period, we included all consecutive patients aged ≥ 18 years that underwent GI cancer surgery and stayed in the SICU for ≥ 24 h. The IPO-Porto Ethics Committee approved this study. The ethical standards displayed in the 1964 Declaration of Helsinki, and its later amendments were followed. Data were made anonymous for analysis.

Demographic and medical information

Demographic and medical information including sex, age, date of hospital admission, diagnosis, type of SICU admission: ward-based postoperative complications or elective surgery (elective), and type of surgery were collected and retrospectively entered into an Excel spreadsheet. We also classified patients according to the P-Possum score (since the POSSUM model overestimates the rate of complications in our sample; data not published), ACS NSQIP (without surgeon adjustment of risk), and ARISCAT Risk predictor. Scoring systems and multivariable analysis from the collected data and medical records according to defined criteria were done. Additionally, we studied POC according to the Clavien-Dindo classification.

Statistical analysis

Continuous variables were described by their median and sample range (min–max). Categorical variables were expressed as actual numbers (*n*) and percentages (%).

To evaluate the association between the occurrence of major complications (Clavien-Dindo ≥ 3) and the potential explanatory variables, we performed a binary logistic regression model. First, considering each variable separately and then making a multivariable model retaining

only the significant variables (MyIPOrisk-score). The predictive ability of each continuous score and the final panel obtained was evaluated using receiving operating characteristic (ROC) curves and estimating the area under the curve (AUC). According to the ROC curve, the cutoff was established in order to maximize the Youden's Index (sensitivity + specificity – 1). Also, the Hosmer–Lemeshow test was used to evaluate the fitted models by comparing the number of predicted complications with the number of observed complications.

We performed a Venn diagram to enhance the relationship between different risk assessment tools in detecting high-risk and low-risk patients as defined by the cutoff value chosen using the criteria explained above. Additionally, we compared the version used in the study with the most recent version announced in the meantime to verify whether the variable serious complications suffered significant changes.

Statistical significance was considered at the level of $P < 0.05$. All statistical analysis was performed using the software R v3.4.4.

Results

Description of the GI cancer patients admitted to the SICU

The characteristics of the patients admitted at the SICU are in Table 1. During the study period, a total of 341 patients (59.8% male) that underwent GI cancer surgery (81.5% elective and 18.5% urgent), were admitted in the SICU. Their ages ranged from 22 to 94, with a mean age of 68 years, and approximately 60% of the patients had an ASA score ≥ III.

The distribution of the performed surgeries was as follows: 103 (30.2%) colorectal surgeries, 60 (17.6%) esophageal-gastric surgeries, 46 (13.5%) hepatic surgeries, 47 (13.8%) urgent laparotomies, 40 (11.7%) hyperthermic intraperitoneal chemotherapy (HIPEC), 19 (5.6%) pancreatic surgeries, and 26 (7.6%) other surgeries.

One hundred and fifteen (33.7%) patients also performed chemotherapy in the preoperative period.

Reasons for admission to the SICU were elective surgeries in patients with comorbidities (59, 17.3%), elective complex surgeries (152, 44.6%), reoperations (63, 18.5%), step-down care (47, 13.7%), and postoperative complications (20, 5.9%).

In the universe of 341 patients, the POC rate was 53.1% (181 patients), and its severity according to Clavien-Dindo's classification was Grade I: 14 (7.7%) patients, Grade II: 82 (45.3%) patients, Grade IIIA: 24 (13.3%) patients, Grade IIIB: 25 (13.8%) patients, Grade IVA: 10 (5.5%) patients, Grade IVB: 12 (6.6%) patients, and Grade V: 14 (7.7%) patients. There were 55 deaths with the following distribution: 12 deaths in the first 30 days (11 were surgical complication related), 10 deaths between the 31st and 90th day (3 were surgical complication related), and 33 deaths after the 90th day.

Table 1 Characteristics of the 341 GI cancer patients admitted at the SICU

Characteristics	No. (%)
Age at admission, mean (min–max)	68 (22–94)
Gender	
F	137 (40.2)
M	204 (59.8)
Neoadjuvant chemotherapy	
No	226 (66.3)
Yes	115 (33.7)
Type of surgery (*n*)	
Elective	278 (81.5)
Reoperations	63 (18.5)
ASA	
2	139 (40.9)
3	176 (51.7)
4	25 (7.4)
Surgical category	
Colorectal	103 (30.2)
Esophageal–gastric	60 (17.6)
Hepatic	46 (13.5)
Urgent laparotomies	47 (13.8)
Hyperthermic intraperitoneal chemotherapy (HIPEC)	40 (11.7)
Pancreatic	19 (5.6)
Other	26 (7.6)
Overall complications	181 (53.1)
Clavien-Dindo classification	
Grade I	14 (7.7)
Grade II	82 (45.3)
Grade IIIA	24 (13.3)
Grade IIIB	25 (13.8)
Grade IVA	10 (5.5)
Grade IVB	12 (6.6)
Grade V	14 (7.7)
Mortality	
30 D	12 (3.5)
90 D	22 (6.5)

F female, *M* male, *D* days

Analysis post-operative complications by risk score

P-POSSUM predicted a more significant proportion of patients at high risk of morbidity (58.5% vs. 25.7%, respectively) and mortality (12.8% vs. 9.7%, respectively) than the ACS NSQIP Risk Calculator. Venn diagrams in Fig. 1 illustrates the relationship between these two risk score tools in

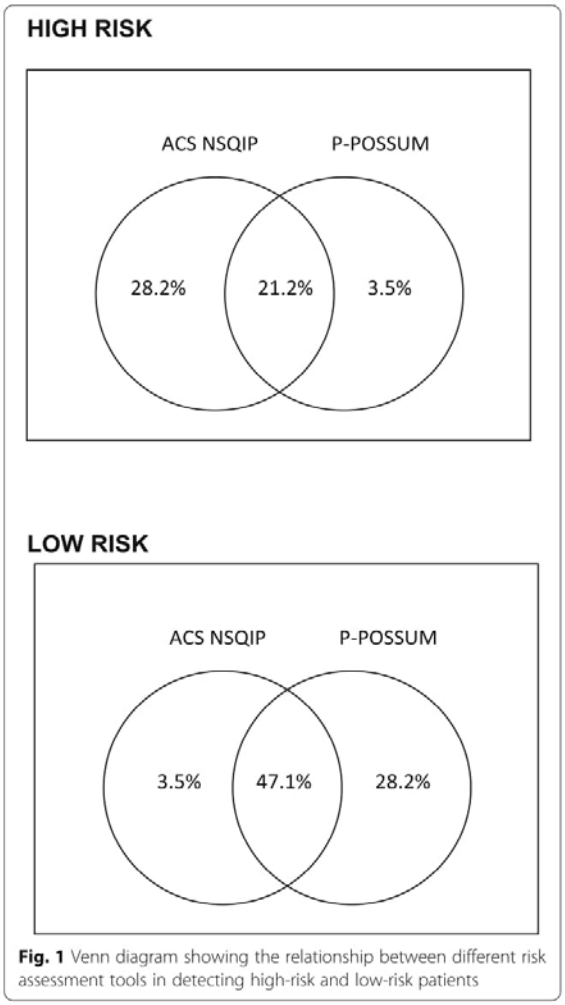

Fig. 1 Venn diagram showing the relationship between different risk assessment tools in detecting high-risk and low-risk patients

detecting patients at high and low risk of developing complications. As shown, only 21.2% ($n = 72$) of patients were classified as high risk and 47.1% ($n = 161$) as low risk by both tools. Comparing the version used in the study with the most recent version in relation to the variable serious complications did not find significant changes.

Regarding pulmonary complications, ACS NSQIP Risk Calculator predicted that 60.4% of patients could develop pneumonia, and ARISCAT predicted that 67.5% of the patients were at risk of respiratory complications. The number of observed respiratory complications was 38 (11.1%), of which 22 (6.4%) required intensive care support.

Comparison of the predicted and observed postoperative complications

The Hosmer–Lemeshow goodness of fit test was used to assess the calibration of the risk scores by comparing the observed with anticipated complications by decile of risk (Tables 2 and 3). P-POSSUM showed excellent performance, with an observed and expected complication ratio ranging from 0.76 to 1.23 and an overall good fit ($\chi^2 = 2.144$; $P = 0.976$). On its turn, ACS NSQIP revealed different results. The number of observed complications was less than expected by this tool in low deciles of risk, while the number of expected complications was more significant than the observed ones in higher deciles of risk. Overall, it presented a significant lack of fit ($\chi^2 = 18.540$; $P = 0.018$).

Multivariable analysis of factors associated with major postoperative complications

Table 4 shows the results of the univariable analysis for major postoperative complications. The significant factors associated with the occurrence of major complications were gender ($P < 0.001$), surgery type ($P < 0.001$), P-POSSUM physiological ($P < 0.001$) and surgical severity ($P < 0.001$), ACS NSQIP ($P < 0.001$), and ARISCAT ($P = 0.001$).

Multivariable logistic regression (Table 5) revealed that occurrence of major complications decreased significantly with age (OR = 0.96; 95%CI: 0.93–0.98), was higher in men (OR = 2.94; 95%CI: 1.52–5.71) and increased with P-Possum (Physiological) score and ACS NSQIP (serious complications) score (OR = 1.08; 95%CI: 1.03–1.12 and OR = 1.06; 95%CI: 1.03–1.09, respectively). We used this model to predict probability of developing postoperative complications and named it as *MyIPOrisk-score*. To dicotomize this score in low/high risk, a cutoff was chosen using the Youden's index. The cutoff obtained was 23.5 being low risk attributed to patients with a score lower than this value. The equation of predicted postoperative complication (*MyIPOrisk-score*) was as follows:

Logit (Postoperative complications) = − 2.39 + (− 0.04) × Age + 1.08 if gender is male + 0.07 × P-POSSUM (Physiological) + 0.06 × ACS NSQIP (Serious complications)

MyIPOrisk-score showed no significant lack of fit (Table 6) ($\chi^2 = 4.44$; $P = 0.815$). The discriminatory ability of the *MyIPOrisk-score* obtained with the final model (AUC = 0.808; 95%CI: 0.755–0.862) was significantly higher than the ability of each score individually (*MyIPOrisk-score* vs. ACS NSQIP: $P = 0.047$; *MyIPOrisk-score* vs. P-Possum: $P = 0.028$) (Fig. 2).

Discussion

In this study, we analyzed and compared the surgical risk obtained by P-POSSUM Scoring, ACS NSQIP Surgical Risk Calculator, and ARISCAT Risk Score according to the outcomes classified by the Clavien-Dindo score. We aimed to evaluate their accuracy as perioperative risk assessment instruments to predict postoperative

Table 2 Hosmer–Lemeshow goodness of fit test for P-Possum for postoperative complications

Deciles of risk (%)	Number of patients	Number of observed complications	Number of expected complications	Mean risk	O:E (95% CI)	X^2HL statistic
0–10	40	4	3.92	0.10	1.02 (0.27–2.61)	0.00
10–20	44	4	5.22	0.12	0.77 (0.21–1.96)	0.32
20–30	24	4	3.26	0.14	1.23 (0.33–3.14)	0.19
30–40	32	6	4.98	0.16	1.20 (0.44–2.62)	0.25
40–50	47	11	9.24	0.20	1.19 (0.59–2.13)	0.42
50–60	27	6	6.30	0.23	0.95 (0.35–2.07)	0.02
60–70	29	6	7.87	0.27	0.76 (0.28–1.66)	0.61
70–80	35	10	11.29	0.32	0.89 (0.42–1.63)	0.22
80–90	33	14	13.80	0.42	1.01 (0.55–1.70)	0.01
90–100	30	20	19.12	0.64	1.05 (0.64–1.62)	0.11
0–100	341	85	85		1.00 (0.80–1.22)	2.14

X^2HL statistic = 2.144; df = 8; $P = 0.976$

morbidity and to identify the most informative variables. Overall, our data suggest that (i) these instruments have a poor predictive performance for POC; (ii) P-POSSUM and ACS NSQIP Risk Calculator have poor agreement for the identification of patients at high risk for morbidity; and (iii) combining the most informative variables of current risk models was superior in predicting POC than each score individually.

The perioperative period is the perfect opportunity to identify patients with increased risk profile for shared and individualized decision-making and preoperative optimization (e.g., prehabilitation) with the ultimate goal of providing better outcomes (Hijazi et al., 2017). For that purpose, several classical risk prediction models (e.g., P-POSSUM Scoring, ACS NSQIP Surgical Risk Calculator, and the ARISCAT Risk Score) were developed and prospectively validated and are currently used worldwide (Huang et al., 2015; Lee et al., 2012; Copeland et al., 1991; Haga et al., 1999; Miki et al., 2014; Kim et al., 2008). However, a significant variation in terms of the diagnostic accuracy of these models has been reported in various surgical specialties, rising doubts about their generalization (Kumagai et al., 2014; Yu et al., 2016; SAH et al., n.d.). We observed a poor accuracy and agreement (below 50%) between the studied models in our cohort of GI cancer patients admitted to the SICU, cautioning us to their routine use to assess preoperative risk for POC and support precision management decisions.

To overcome this limitation, we performed this training set study and identified the most informative variables from current risk models assessed in our study, with major complications (Clavien-Dindo ≥ 3) as the outcome measure of reference. Binary logistic regression identified that the occurrence of major complications decreased significantly with age (OR = 0.96; 95%CI:

Table 3 Hosmer–Lemeshow goodness of fit test for ACS NSQIP for postoperative complications

Deciles of risk (%)	Number of patients	Number of observed complications	Number of expected complications	Mean risk	O:E (95% CI)	X^2HL statistic
0–10	34	1	2.12	0.06	0.47 (0.01–2.63)	0.63
10–20	35	2	3.00	0.09	0.67 (0.07–2.41)	0.37
20–30	33	2	3.62	0.11	0.55 (0.06–1.99)	0.82
30–40	34	8	4.98	0.15	1.61 (0.69–3.17)	2.15
40–50	36	3	6.29	0.17	0.48 (0.10–1.39)	2.09
50–60	32	10	6.71	0.21	1.49 (0.71–2.74)	2.04
60–70	34	15	8.72	0.26	1.72 (0.96–2.84)	6.08
70–80	35	10	11.13	0.32	0.90 (0.43–1.65)	0.17
80–90	33	9	14.69	0.45	0.61 (0.28–1.16)	3.98
90–100	34	25	23.73	0.70	1.05 (0.68–1.56)	0.22
0–100	340	85	85		1.00 (0.80–1.22)	18.54

X^2HL statistic = 18.540; df = 8; $P = 0.018$

Table 4 Association between explanatory variables and major postoperative complications (Clavien-Dindo ≥ 3)

Variable	OR (95% CI)	*P* value
Age	0.99 (0.97–1.01)	0.240
Gender		
F	1	
M	3.53 (1.97–6.34)	< 0.001
Neoadjuvant chemotherapy		
No	1	
Yes	0.66 (0.38–1.14)	0.135
Surgery type		
Elective	1	
Reoperations	7.47 (4.12–13.53)	< 0.001
ASA		
2	1	
3	1.67 (0.94–2.95)	0.080
4	21.27 (7.22–62.68)	< 0.001
P-Possum		
Physiological	1.11 (1.07–1.15)	< 0.001
Surgical severity	1.20 (1.14–1.27)	< 0.001
ACS NSQIP	1.09 (1.06–1.11)	< 0.001
ARISCAT	1.03 (1.01–1.05)	0.001

F female, *M* male

0.93–0.98), was higher in men (OR = 2.94; 95%CI: 1.52–5.71) and increased with P-Possum (Physiological) score and serious complications ACS score (OR = 1.08; 95%CI: 1.03–1.12 and OR = 1.06; 95%CI: 1.03–1.09, respectively). The decrease of risk with age is probably explained by the avoidance of complex surgical procedures performed in older patients. When considered alone, the ARISCAT score was also associated with the occurrence of major complications but lost significance after adjusting for the other variables. Our results are in agreement with Scott S et al. (Scott et al., 2014), who found that the Physiological score of POSSUM and P-POSSUM had higher discrimination than the Operative score in predicting postoperative mortality at a critical care setting. We did not find significant POC variation according to age and gender, although there are references in the literature about a relative preponderance in young patients undergoing surgery for GI cancer, probably due to more extensive operations to which they are submitted. As for gender discrimination, it seems to depend more on the type of tumor involved (Alves et al., 2002; Knoferl et al., 2002; Schroder et al., 1998).

Table 5 Significancy of variables involved in MyIPOriskScore

Variables	OR	95% CI for OR	
		Lower	Upper
Age	0.96	0.93	0.98
Gender (M/F)	2.94	1.52	5.71
PP (physiological)	1.08	1.03	1.12
ACS NSQIP (serious complication)	1.06	1.03	1.09

F female, *M* male

Choi M et al., when testing the potential feasibility of the ACS NSQIP Surgical Risk Calculator for predicting long-term cancer outcomes in patients with resected pancreatic head cancer, found that the serious complication rate parameter calculated with this risk assessment instrument was the most informative (Choi et al., 2019).

Based on the informative variables of current risk models, we constructed a model with a greater accuracy to predict complications in the postoperative period in GI cancer patients in need of surgery, that we named *MyIPOrisk-score*. The discrimination ability of the *MyIPOrisk-score* obtained with the final model (AUC = 0.808; 95%CI: 0.755–0.862) was significantly higher than each score individually (*MyIPOrisk-score* vs ACS NSQIP: $P = 0.047$; *MyIPOrisk-score* vs P-Possum: $P = 0.028$). These results are very similar to those recently published by Bihorac A et al. (Bihorac et al., 2019) that developed and validated, in a cohort of 51,457 surgical patients undergoing major inpatient surgery, an automated analytics framework for a preoperative risk algorithm to forecast patient-level probabilistic risk scores for 8 major postoperative complications (acute kidney injury, sepsis, venous thromboembolism, intensive care unit admission > 48 h, mechanical ventilation > 48 h, wound, neurologic, and cardiovascular complications) and death up to 24 months after surgery. This model calculates probabilistic risk scores for 8 postoperative complications with AUC values ranging between 0.82 and 0.94 (99% confidence intervals (CIs) 0.81–0.94). (Schroder et al., 1998) Importantly, the Hosmer–Lemeshow equation revealed that *MyIPOrisk-score* presented the best association between the number of observed complications and the number of expected complications.

Our study is not free of limitations. It was a single-center retrospective study, and some of the data were collected from medical records, which could be a source of bias due to the need of interpreting data. NSQIP may change their model discrimination or calibration. However, our results did not present any quality change when we used the latest versions of this score and compared with the previous (the rate of serious complications is stable). Although *MyIPOrisk-score* needs other scores to obtain a prediction, these are available for everyone. The feasibility of the *MyIPOrisk-score* now requires further testing through multicenter prospective studies to validate the predictive accuracy of the proposed risk score.

Table 6 Hosmer–Lemeshow goodness of fit test for MyIPOriskScore for postoperative complications

Deciles of risk (%)	Number of patients	Number of observed complications	Number of expected complications	Mean risk	O:E (95% CI)	X^2HL statistic
0–10	34	2	1.15	0.03	1.75 (0.20–6.30)	0.66
10–20	34	0	2.07	0.06	0.00 (-)	2.20
20–30	34	3	3.06	0.09	0.98 (0.20–2.86)	0.00
30–40	34	4	4.01	0.12	1.00 (0.27–2.55)	0.00
40–50	34	7	5.25	0.15	1.33 (0.53–2.75)	0.69
50–60	34	8	6.34	0.19	1.26 (0.54–2.49)	0.53
60–70	34	7	8.40	0.25	0.83 (0.33–1.72)	0.31
70–80	34	11	10.91	0.32	1.01 (0.50–1.80)	0.00
80–90	34	16	16.42	0.48	0.97 (0.56–1.58)	0.02
90–100	34	27	27.39	0.81	0.99 (0.65–1.43)	0.03
0–100	340	85	85		1.00 (0.80–1.22)	4.44

X^2HL statistic = 4.440; df = 8; $P = 0.815$

The main interest in the use of this score is to identify more accurately patients with high risk of having postoperative complications so that they can be subjected to a prehabilitation program in order to optimize their performance in preoperative time and a postoperative care in the SICU.

Conclusion

Based on the most informative variables of current risk models, we developed a surgical risk score instrument that showed greater performance in predicting risk of surgical complications in GI cancer surgeries. However, it will be necessary to evaluate its performance using a validation set.

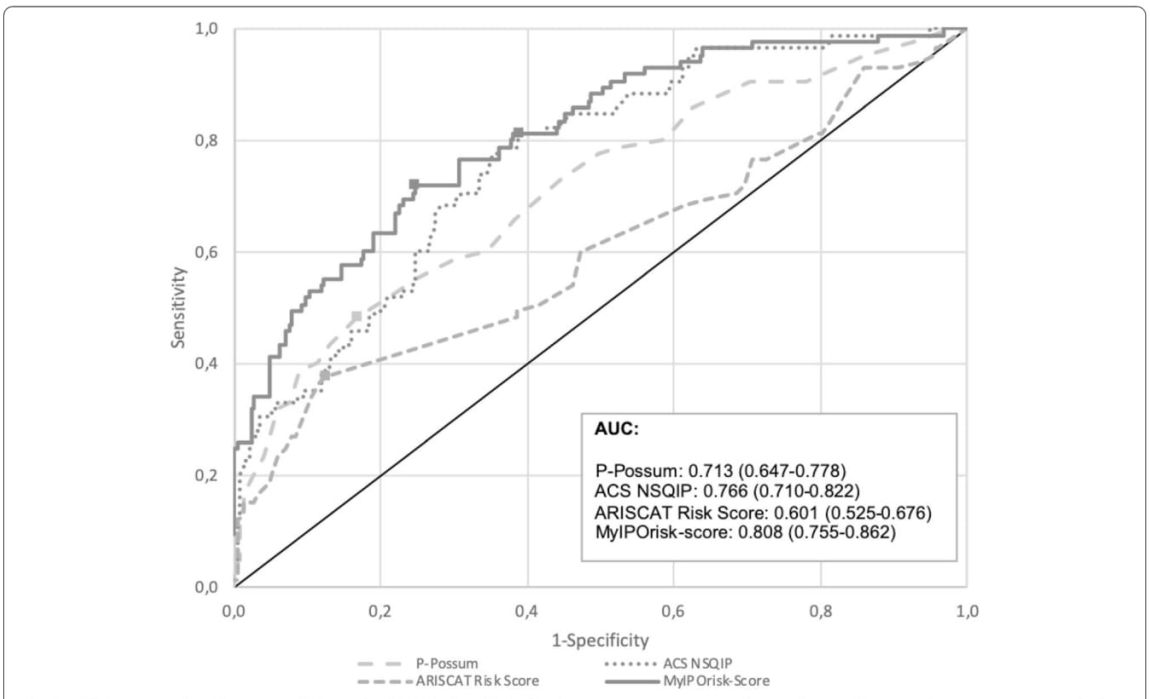

Fig. 2 ROC curve for the P-Possum, ACS NSQIP, ARISCAT, and MyIPOrisk-score scoring systems for predicting the rate of postoperative morbidity (i.e., complications according to the Clavien-Dindo classification) in patients undergoing GICS. *ROC* receiver operating characteristic, *AUC* area under the curve

Abbreviations
ACS NSQIP: American College of Surgeons National Surgical Quality Improvement Program; AUC: Area under the curve; ASA PS: Anesthesiologists Physical Status classification system; ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia; GI: Gastrointestinal; GICS: GI cancer surgery; IPO-Porto: Portuguese Oncology Institute of Porto, Portugal; MyIPOrisk-score: Our new risk score; POC: Postoperative complications; P-Possum: Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) and Portsmouth-POSSUM *scores*; ROC curves: Receiver operating characteristic curves; SICU: Surgical Intermediate Care Unit

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Authors' contributions
AF and LLS were responsible for the primary conception and design of the article with input from co-authors. Initial drafts of the paper were prepared by LLS, AF, JR, LA, DMG, and CSS. Additions, modifications, and revisions critical for the relevant intellectual content of the article were performed by LLS, AF, PL, RC, DMG, MDR, and JAS. All approved the final version to be published.

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The datasets generated and/or analyzed during the current study are available in the IPO-PORTO repository. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The IPO-Porto Ethics Committee approved this study. The ethical standards displayed in the 1964 Declaration of Helsinki and its later amendments were followed. Data were made anonymous for analysis.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

3.2 Causas e evolução das complicações pulmonares pós-operatórias após cirurgia abdominal: estudo de coorte observacional retrospetivo

As complicações pulmonares pós-operatórias contribuem significativamente para a morbimortalidade perioperatória geral. Na cirurgia abdominal, as complicações pulmonares pós-operatórias são muito frequentes. Este estudo teve como objetivo analisar o perfil e as consequências das complicações pulmonares pós-operatórias em doentes submetidos a cirurgia abdominal e admitidos numa unidade de Cuidados Intensivos Polivalente em Portugal.

Metodologia:
De janeiro a dezembro de 2017, na unidade de cuidados intensivos polivalente do Hospital Garcia de Orta, Almada, Portugal, realizamos um estudo observacional retrospetivo de doentes admitidos e submetidos a cirurgia abdominal urgente ou eletiva e que desenvolveram complicações pulmonares pós-operatórias graves. Foram avaliados os fatores de risco perioperatórios e a mortalidade associada. Com recurso à regressão logística tentámos identificar os fatores de risco perioperatórios mais importantes na génese de complicações pulmonares pós-operatórias.

Resultados:
Sessenta doentes (75% do sexo masculino) submetidos a cirurgia abdominal urgente ou eletiva foram incluídos na análise, a idade média da amostra foi de 64,5 (47-81) anos. Trinta e seis doentes (60%) desenvolveram complicações pulmonares nas primeiras 48 horas pós-operatórias e 24 desenvolveram complicações pulmonares pós-operatórias após 48 horas. A pneumonia foi a complicação pulmonar pós-operatória mais frequente nesta amostra. Nesta coorte, 48 doentes desenvolveram insuficiência respiratória aguda e necessitaram de ventilação mecânica. No cenário de emergência, a peritonite associou-se a maior taxa de complicações pulmonares no pós-operatório.

Doentes operados de forma eletiva que desenvolveram complicações pulmonares no pós-operatório eram na sua maioria portadores de cancro digestivo. A mortalidade aos trinta dias foi de 21,7%. O risco de desenvolvimento de complicações pulmonares no pós-operatório nas primeiras 48 horas esteve associado à necessidade de utilização de bloqueadores neuromusculares várias vezes durante a cirurgia e a gasimetrias arteriais alteradas no pré-operatório. A incisão cirúrgica abdominal mediana, cirurgias prolongadas e um índice de massa corporal elevado foram associados a complicações pulmonares pós-operatórias que ocorreram 48 horas após a cirurgia. Doentes com ASA 4 e com história de DPOC ou Asma tiveram menos necessidade de ventilação mecânica no tratamento das complicações respiratórias, o que parece dever-se ao facto de terem otimizados no pré-operatório. A desnutrição (baixa albumina) prévia à cirurgia associou-se a mortalidade em 30 dias.

Conclusões:

As complicações pulmonares após cirurgia abdominal continuam a representar um problema significativo, exercendo um impacto muito negativo no prognóstico clínico pós-operatório. Os nossos resultados sugerem que os programas de intervenção prévios à cirurgia, envolvendo mudanças de estilo de vida pré-operatórias, como suplementação nutricional, exercício, redução do stress e cessação tabágica, foram uma estratégia eficaz na mitigação de complicações pós-operatórias, diminuindo a mortalidade.

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Root causes and outcomes of postoperative pulmonary complications after abdominal surgery: a retrospective observational cohort study

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Abstract

Background: Postoperative pulmonary complications (PPCs) contribute significantly to overall postoperative morbidity and mortality. In abdominal surgery, PPCs remain frequent. The study aimed to analyze the profile and outcomes of PPCs in patients submitted to abdominal surgery and admitted in a Portuguese polyvalent intensive care unit.

Methods: From January to December 2017 in the polyvalent intensive care unit of Hospital Garcia de Orta, Almada, Portugal, we conducted a retrospective, observational study of inpatients submitted to urgent or elective abdominal surgery who had severe PPCs. We evaluated the perioperative risk factors and associated mortality. Logistic regression was performed to find which perioperative risk factors were most important in the occurrence of PPCs.

Results: Sixty patients (75% male) with a median age of 64.5 [47–81] years who were submitted to urgent or elective abdominal surgery were included in the analysis. Thirty-six patients (60%) developed PPCs within 48 h and twenty-four developed PPCs after 48 h. Pneumonia was the most frequent PPC in this sample. In this cohort, 48 patients developed acute respiratory failure and needed mechanical ventilation. In the emergency setting, peritonitis had the highest rate of PPCs. Electively operated patients who developed PPCs were mostly carriers of digestive malignancies. Thirty-day mortality was 21.7%. The risk of PPCs development in the first 48 h was related to the need for neuromuscular blocking drugs several times during surgery and preoperative abnormal arterial blood gases. Median abdominal surgical incision, long surgery duration, and high body mass index were associated with PPCs that occurred more than 48 h after surgery. The American Society of Anesthesiologists physical status score 4 and COPD/Asthma determined less mechanical ventilation needs since they were preoperatively optimized. Malnutrition (low albumin) before surgery was associated with 30-day mortality.

Conclusion: PPCs after abdominal surgery are still a major problem since they have profound effects on outcomes. Our results suggest that programs before surgery, involve preoperative lifestyle changes, such as nutritional supplementation, exercise, stress reduction, and smoking cessation, were an effective strategy in mitigating postoperative complications by decreasing mortality.

Keywords: Abdominal surgery, Acute respiratory failure, Mechanical ventilation, Polyvalent intensive care unit, Postoperative pulmonary complications, Risk score

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Background

Nearly 234 million patients undergo major surgery worldwide every year [1]. Approximately 16% will suffer a complication within 30 days [2]. In 2015, the European Perioperative Clinical Outcome (EPCO) standardized the concept of postoperative complications (POCs) in the various organ systems, which constitutes an important advance in perioperative medicine [3]. One set of under-reported complications are postoperative pulmonary complications (PPCs) that are costly and increase patient mortality. After abdominal surgery (AS), PPCs are one of the most important causes of postoperative morbidity and mortality [4, 5]. Various perioperative risk factors are related to their appearance in the postoperative period [6]. Physiological changes in the respiratory system that occur immediately after the induction of general anesthesia explain the majority of POCs [7]. Thus, respiratory drive and muscle function are altered, lung volumes reduced, and atelectasis develops in more than 75% of patients receiving neuromuscular blocking drugs (NMBD). The respiratory system may take 6 weeks to return to its preoperative state after general anesthesia for major surgery [8]. Acute respiratory failure (ARF) is common in intensive care settings and classified by some studies as a PPC on its own, and in some patients its severity that may lead to the need for mechanical ventilation (MV) as a method of respiratory support [9]. Previous respiratory pathology, obesity, and nutritional deficits also contribute significantly to the occurrence of respiratory complications in the postoperative period. Some of these factors are modifiable [10, 11]. Facing the magnitude of PPCs, performing an early identification of surgical patients at risk for ARF would allow to intervene in an earlier and most useful time, increasing the survival of these patients [12–17]. The American Society of Anesthesiologists physical status (ASA PS) and ARISCAT score (for PPCs), while effective risk prediction tools, can help reduce morbidity and mortality [18, 19]. However, there are few prospective comparative studies of accuracy between them, and this knowledge is still poorly investigated [20, 21]. The rationale of this study was to analyze the incidence, precocity, profile and the outcome impact of PPCs in patients who underwent AS and were admitted in a PICU (polyvalent intensive care unit) in order to find strategies that minimize their mortality.

Methods

Study patients were included from a universe of medical and surgical patients hospitalized in PICU of Hospital Garcia de Orta, Almada, Portugal, from January to December 2017. Sixty patients who were submitted to an urgent or elective AS and developed PPCs in the postoperative period leading to severe ARF despite the need for MV were retrospectively analyzed. The admission criteria in PICU were the surgical complexity level 4 and 5 according to L. R. Pasternak classification (meaning highly invasive procedure, duration of surgery and intraoperative complications with usual postoperative PICU stay with invasive monitoring) and severity criteria (Table 1) of the patient [22]. All patients received standard clinical care and no research-related intervention was introduced. An experienced chest physician assessed the postoperative respiratory status of all patients. We collected data on the occurrence (≤48 h and > 48 h) of symptomatic and clinically significant PPCs using clinical, laboratory, and radiology data. We evaluated perioperative risk factors associated with PPCs, namely age and gender, body mass index (BMI), previous history of chronic obstructive pulmonary disease (COPD), serum albumin, type of anesthesia (general versus spinal anesthesia), type of surgery (laparotomy versus laparoscopy), use of NMBD during perioperative period, incision type, surgical intervention time and surgical procedure in urgent or elective context. PPCs have been defined according to EPCO and were diagnosed by clinical and radiological examinations and arterial blood gases (ABG), examined using the ABL 555 analyzer (Radiometer, Copenhagen, Denmark). Using clinical records, the risk of PPC was retrospectively estimated according to ASA PS and ARISCAT scores, and this data was compared with the real incidence. Right after surgery and 48 h after AS, pulmonary examinations of patients were repeated and when PPCs were present the following classifications were registered:

1. Atelectasis (by thoracic ultrasound, CT scan and/or x-ray evidence of the collapse of the alveoli, lung opacification with the shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory over inflation in the adjacent non-atelectatic lung);
2. Bronchospasm (newly detected expiratory wheezing treated with bronchodilators), pleural effusion (chest radiograph demonstrating; blunting of the costophrenic angle, evidence of displacement of adjacent anatomical

Table 1 Severity criteria on admission, PICU Length of stay and mortality of patients undergoing AS

Admitted patients	60 cases
PICU hospitalization time in days (median, min-max)	6.31 days [0.8–21]
APACHE II (mean ± standard deviation)	22.8 ± 8.1points
SAPS II (mean ± standard deviation)	50.7 ± 17.9points
PICU Mortality rate (n, %)	21.7% (13 patients)
Hospital mortality rate (n, %)	36.7% (22 patients)
SMR for SAPS II (median, min-max)	0.68 points [0.53–0.74]
Readmission rate < 48 h (%)	0.9%
VAP, number of episodes/1000 days of IT (median, min-max)	8.7 [7.1–10.3]

APACHE Acute Physiology, Age, Chronic Health Evaluation, *AS* abdominal surgery, *IT* tracheal intubation, *PICU* polyvalent intensive care unit, *PPCs* Postoperative pulmonary complications, *SAPS* Simplified Acute Physiology Score, *SMR* Standardized Mortality Rate, *VAP* ventilator-associated pneumonia

structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows);

3. Pneumothorax (a collection of air in the pleural space - an area with no vascular bed surrounding the visceral pleura);

4. Acute Respiratory Distress Syndrome (ARDS) diagnosed by criteria of Berlin definition 2012 [23];

5. Pulmonary emboli (diagnosed if a patient had suggestive clinical findings, blood gas abnormality, consistent image of a pulmonary embolism on computed tomography with intravenous contrast);

6. Pneumonia (diagnosed if a patient had clinical, laboratory and/or radiological evidence of consolidation or infiltration not present in the preoperative chest roentgenograms), with or without positive cultures;

7. Tracheobronchitis (diagnosed if the patient had clinical, laboratory and no radiological evidence of consolidation or infiltration in chest roentgenograms);

8. Aspiration pneumonitis (acute lung injury after the inhalation of regurgitated gastric contents);

9. ARF (postoperative arterial oxygen pressure (PaO2) < 60 mmHg on room air, a ratio of PaO2 to inspired oxygen fraction (FiO2) < 300, or arterial oxygen saturation (SaO2) < 90% and requiring oxygen therapy).

10. Patient optimization means control of chronic diseases and kinesiotherapy.

11. The term "prehabilitation", is a combination of the words "pre- "and "rehabilitation". Prehabilitation concerns a combination of preparational and post-procedure measures to improve the outcome of a planned procedure, such as major surgery. Prehabilitation programs are used to improve postoperative outcomes. These programs before surgery, involve preoperative lifestyle changes, such as nutritional supplementation, exercise, stress reduction, and smoking cessation. Therefore structured and sustained exercise over a period of few weeks leads to improved cardiovascular, respiratory, and muscular conditioning.

The incidence of PPCs, the profile and the postoperative mortality associated defined as death within 30 days of surgery were also evaluated.

All statistical analyses were performed with R Statistical software (version 3.6.0). Continuous variables were described using median and range or mean ± standard deviation, and categorical variables were expressed as frequencies or percentages. Student's t-tests were used for comparing continuous variables, and chi-squared tests or Fisher's exact tests were used for comparing categorical data. A p-value of < 0.05 was considered to be statistically significant. Logistic regression was performed to determine which perioperative risk factors were associated with the development of PPCs.

The Ethics Committee of Hospital Garcia de Orta approved the study protocol.

Results

In our sample, 45 (75%) males and 15 (25%) females, with a median (min-max) age of 64.5 years (47–81) were submitted to urgent or elective abdominal surgery. Severity criteria on admission, PICU Length of stay and mortality of patients undergoing AS are shown in Table 1. Thirty six patients underwent emergency surgery and the remaining 24, elective surgery (Table 2).

PPC group description

Thirty-six patients (60%) developed PPCs within 48 h, from which 29 (80.6%) were male. The median (min-max) age was 65 (54–81) years. Twelve patients (20%) developed additional PPCs related with invasive ventilation side effects after 48 h. Twenty-four (40%) only developed PPCs after 48 h. From these, 16 (66.7%) were male. The median (min-max) age was 64.5 (49–81) years. We did not find significant differences in the median age of the two groups ($p = 0.2$).

Pneumonia was the most frequent PPC in the sample (PPCs ≤48 h and > 48 h; Fig. 1). Regarding the patients who developed additional PPCs after 48 h, the complications were 7 tracheobronchitis, 6 bronchospasms, 5 atelectasis, 5 ARDS, 3 pleural effusion and 1 pneumothorax.

In the emergency setting, peritonitis had the highest rate of PPCs. The group of electively treated patients who developed PPCs was mostly carriers of digestive malignancies (Table 2).

Perioperative relevant risk factor for the development of PPCs

Regarding the preoperative variables and the risk of PPCs, we verified that the knowledge of ASA score 4 before surgery associated with measures to optimize performance status revealed to be a PPC protection factor (OR = 0.04; 95%CI: 0.01–0.28). Patients with a high risk ARISCAT score also showed a reduced risk of developing PPCs after 48 h (OR = 0.17; 95%CI: 0.03–0.88). In this group of patients, preoperative performance status optimization and/or early diagnosis of pulmonary impairment reflected a reduced risk of PCCs, as we mentioned before. A significantly lower risk of PCCs was also observed for patients undergoing a median surgical incision, in the first 48 h (OR = 0.22; 95%CI: 0.06–0.79), and for patients with more time-consuming surgeries, after 48 h (OR = 0.29; 95%CI: 0.09–0.90). In contrast, patients with pre-operative abnormal arterial blood gases prior to surgery (OR = 3.50; 95%CI: 1.14–10.74) or who required NMBD several times intraoperatively had a higher risk of PPCs in the first 48 h (OR = 18.40; 95%CI: 2.24–151.35). High BMI was significantly associated with the occurrence of PPCs after 48 h (OR = 15.40; 95%CI: 1.47–160.97) (Table 3).

Table 2 AS etiology in patients with PPCs

Etiology	Patients (n, %)	Emergency surgery (n, %)		Elective surgery (n, %)	
		≤48 h	> 48 h	≤48 h	> 48 h
Peritonitis	11 (18.3)	9 (15.0)	2 (3.3)	–	–
Colorectal cancer	9 (15.0)	–	2 (3.3)	7 (11.7)	–
Mesenteric ischemia	8 (13.3)	1 (1.7)	7 (11.7)	–	–
Cholangiocarcinoma	5 (8.3)	–	–	3 (5.0)	2 (3.3)
Bowel obstruction	4 (6.7)	3 (5.0)	1 (1.7)	–	–
Abdominal trauma	3 (5.0)	2 (3.3)	1 (1.7)	–	–
Acute Pancreatitis	3 (5.0)	–	3 (5.0)	–	–
Gastric cancer	5 (8.3)	–	–	4 (6.7)	1 (1.7)
Esophageal cancer	5 (8.3)	–	–	5 (8.3)	–
Cholecystitis	5 (8.3)	2 (3.3)	3 (5.0)	–	–
Diverticulitis	1 (1.7)	–	–	–	1 (1.7)
Abdominal aortic aneurysm	1 (1.7)	–	–	–	1 (1.7)

No significant differences in APACHE and SAPS scores were found between the patients that developed PPCs in the first 48 h and the group of patients that only developed PPCs after 48 h (APACHE: $p = 0.829$; SAPS: $p = 0.378$) (Table 4).

Mechanical ventilation and mortality relevant factors

In our sample, 48 patients developed ARF and needed mechanical ventilation, 23 (47.9%) patients within 24 h and 25 (52.1%) after 24 h. In only 1 of these patients, a non-invasive method was the first attempt. Patients with COPD or asthma history and optimized ASA score 4 were less ventilated. All cases with elevated lactate 12 h after surgery developed PPCs and required ventilation. Patients with proven respiratory infection required ventilation within 24 h.

Thirty-day mortality of patients with PPCs was analyzed and its association with the APACHE II and SAPS II scores were assessed. No significant association was found between these scores and 30-day mortality. Mortality was lower in optimized patients (ASA 4: $p = 0.04$). Patients with albumin deficiency before surgery had major and significant mortality in the first 30 days after surgery ($p = 0.01$).

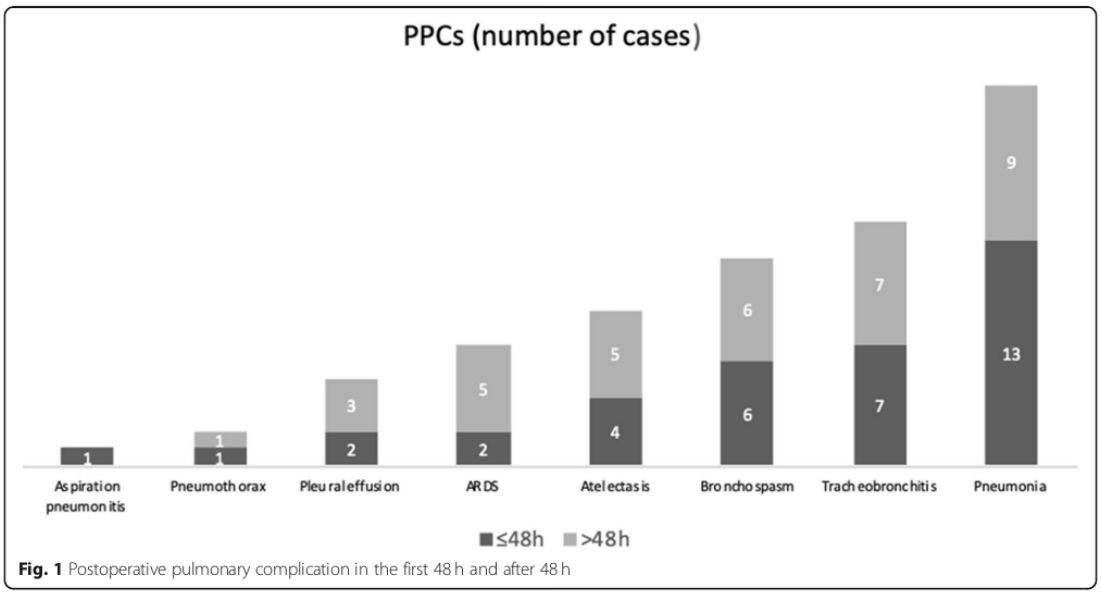

Fig. 1 Postoperative pulmonary complication in the first 48 h and after 48 h

Table 3 Potential perioperative risk factors and PPCS, Mechanical Ventilation and 30-day mortality

Variable	n	PPC (Postoperative Pulmonary Complications)		Mechanical Ventilation	30-Day Mortality
		≤ 48 h	> 48 h		
		OR (95% C.I.)[a]	OR (95% C.I.)[a]	OR (95% C.I.)[a]	OR (95% C.I.)[a]
Sex					
M	45	1	1	1	1
F	15	0.48 (0.15–1.58)	3.50 (0.87–14.11)	0.59 (0.15–2.35)	2.31 (0.62–8.64)
NMBD					
No	43	1	1	1	1
Yes	17	**18.40 (2.24–151.35)**	0.67 (0.21–2.08)	**	2.81 (0.78–10.12)
Age	60	1.05 (0.98–1.13)	0.95 (0.89–1.03)	1.01 (0.93–1.10)	1.05 (0.97–1.15)
ASA					
1	18	1	1	1	1
2	17	0.37 (0.07–1.80)	0.56 (0.14–2.21)	0.94 (0.05–16.35)	1.09 (0.27–4.41)
3	13	0.32 (0.06–1.70)	0.31 (0.07–1.38)	0.13 (0.01–1.37)	0.17 (0.02–1.60)
4	12	**0.04 (0.01–0.28)**	2.50 (0.41–15.23)	**0.06 (0.01–0.59)**	**
ARISCAT					
Low risk < 26	14	1	1	1	1
Intermediate Risk 26–44	16	1.65 (0.37–7.37)	0.21 (0.04–1.29)	0.72 (0.10–5.09)	1.50 (0.32–6.99)
High risk > 45	30	0.98 (0.27–3.53)	**0.17 (0.03–0.88)**	0.55 (0.10–3.06)	0.28 (0.05–1.47)
Respiratory Infection					
No	50	1	1	1	1
Yes	10	1.00 (0.25–4.00)	1.69 (0.39–7.31)	2.54 (0.29–22.27)	1.71 (0.38–7.84)
Anemia					
No	30	1	1	1	1
Yes	30	0.76 (0.27–2.13)	2.33 (0.81–6.73)	1.00 (0.28–3.54)	1.22 (0.36–4.17)
Incision Type					
Bilateral subcostal	21	1	1	1	1
Median	39	**0.22 (0.06–0.79)**	**4.14 (1.34–12.72)**	0.13 (0.02–1.07)	0.55 (0.16–1.91)
LPT vs. LPC					
LPC (Laparoscopy)	19	1	1	1	1
LPT (Laparotomy)	41	1.14 (0.38–3.43)	1.14 (0.38–3.43)	1.73 (0.47–6.40)	0.45 (0.13–1.58)
Surgery Duration					
< 180 min	42	1	1	1	1
> 180 min	18	3.18 (0.90–11.28)	**0.29 (0.09–0.90)**	2.50 (0.49–12.79)	2.50 (0.70–8.92)
Smokers					
No	35	1	1	1	1
Yes	25	1.33 (0.46–3.83)	0.75 (0.26–2.14)	1.00 (0.28–3.61)	0.55 (0.15–2.04)
BMI					
< 18	12	1	1	1	1
18–25	20	0.78 (0.15–3.93)	1.40 (0.33–5.93)	**	0.75 (0.14–4.13)
25–30	16	0.56 (0.11–2.90)	2.33 (0.51–10.78)	**	1.36 (0.25–7.32)
30–35	12	**0.11 (0.02–0.71)**	**15.40 (1.47–160.97)**	**	0.27 (0.02–3.09)
COPD/Asthma History					
No	42	1	1	1	1
Yes	18	0.56 (0.18–1.70)	2.15 (0.65–7.11)	**0.21 (0.06–0.80)**	1.63 (0.45–5.92)

Table 3 Potential perioperative risk factors and PPCS, Mechanical Ventilation and 30-day mortality *(Continued)*

Variable	n	PPC (Postoperative Pulmonary Complications)		Mechanical Ventilation	30-Day Mortality
		≤ 48 h	> 48 h		
		OR (95% C.I.)[a]	OR (95% C.I.)[a]	OR (95% C.I.)[a]	OR (95% C.I.)[a]
POSA					
≤ 35 g/L	8	5.55 (0.64–48.41)	0.63 (0.14–2.79)	1.88 (0.21–16.92)	**19.29 (3.23–115.22)**
> 35 g/l	52	1	1	1	1
Lactate					
< 4 mmol/l	14	1	1	1	1
> 4 mmol/l	46	0.52 (0.14–1.90)	1.17 (0.35–3.92)	**	0.38 (0.10–1.44)
PREOP Abnormal Arterial blood gases					
No	20	1	1	1	1
Yes	40	**3.50 (1.14–10.74)**	**0.16 (0.04–0.63)**	1.57 (0.43–5.77)	0.49 (0.14–1.74)
Pa02 ≤ 50 ≥ 60 Moderate - Severe ARF					
No	25	1	1	1	1
Yes	35	2.36 (0.82–6.83)	0.41 (0.14–1.23)	1.53 (0.43–5.44)	1.82 (0.49–6.74)
Pa02/FiO2					
< 100	21	0.83 (0.28–2.45)	1.13 (0.38–3.35)	1.80 (0.43–7.53)	**
101–300	39	1	1	1	1
PREOP Abnormal Chest radiography					
No	36	1	1	1	1
Yes	24	3.00 (0.97–9.30)	0.37 (0.13–1.09)	4.23 (0.84–21.40)	2.06 (0.59–7.13)

ASA PS American Society of Anesthesiologists physical status, *BMI* body mass index, *COPD* Chronic Obstructive Pulmonary Disease, FiO_2 Inspiratory oxygen fraction, *LPC* Laparoscopy, *LPT* Laparotomy, *NMBD* Neuromuscular blocking drugs, PaO_2 arterial oxygen pressure, *PREOP* preoperative period, *POSA* preoperative serum albumin. a Unadjusted (Univariable Model);** No cases in at least one of the groups; Bold - significant values.

Discussion

To the best of our knowledge, this is the first study that evaluates the profile of PPCs in a population submitted to abdominal surgery in Portugal. We observed that PPCs occur within 48 h in 60% of abdominal surgical patients that need ICU care in the immediate postoperative period. Patients operated in an emergency setting for peritonitis had the highest rate of PPCs. In the elective setting, patients who were operated due to a digestive cancer were more prone to a PPC. Forty-eight patients developed ARF. In accordance with our results, the report of Serejo et al. [24] recorded a 28.2% incidence of pulmonary complications, in patients undergoing emergency abdominal surgery. Kumar et al. studied one hundred and fifty patients who underwent abdominal surgery, and of these, 16% developed PPCs and the highest incidence occurred in the emergency surgery group too [25]. Verma et al. conducted a study of PPCs in patients of emergency abdominal surgeries and found that pre-operative abnormal chest X-ray changes were 3 times more common in the PPCs group as compared to the control group without PPCs [26]. In our study, no significant association was observed between this variable and the occurrence of PPCs. On the other hand, regarding elective surgery, Yang and colleagues [6] confirmed this finding, reporting a higher incidence of PPCs in esophagectomy and other upper abdominal procedures as we found in our series.

We observed that patients with ASA score 4 and high-risk ARISCAT score before surgery had a lower risk of complications within the first 48 h and after 48 h, respectively, as they were previously optimized. Low

Table 4 PPCs, 30-day mortality and Severity Indices

Patients undergoing AS	Patients number (%)	30-day mortality	APACHE II (mean)	SAPS II (mean)
OP	60 (100)	21.7%	22.8 ± 8.1*	50.7 ± 17.9*
PPCs ≤48 h	36 (60)	27.8% (10 patients)	23.0 ± 6.5**	49.0 ± 17.3**
PPCs > 48 h	24 (40)	12.5% (3 patients)	22.5 ± 10.2**	53.2 ± 18.9**

APACHE Acute Physiology, Age, Chronic Health Evaluation, *AS* abdominal surgery, *OP* operated patients, *PPCs* postoperative pulmonary complications, *SAPS* Simplified Acute Physiology Score; * (APACHE: $p = 0.829$; SAPS: $p = 0.378$). ** statistically not significant

albumin levels were found to be poor prognostic factor. It is important to underline that in cases of emergency surgery we cannot modify these risk factors. However, in elective surgery, even in digestive oncological diseases, we have time to optimize these patients. In this sense, there is evidence that prehabilitation programs reduced the risk of complications including respiratory ones [27] and such a prehabilitation program is being implemented in our Institutions.

High ARISCAT score, high BMI, pre-operative abnormal arterial blood gases, and albumin deficiency before surgery can be a surrogate marker for prehabilitation measures to improve their prevention. In several studies, the ARISCAT score has proved its efficacy in the identification of PPCs risk in the surgical population, including the population submitted to abdominal surgery. This score was already validated for the Portuguese population [28, 29].

We found that, in the first 48 h after ICU admission, the identification of lactate acidemia or pre-operative abnormal arterial blood gases plays an important role in therapeutic measures with a positive impact on the outcome of these patients. In the group that needed ventilation 24 h after surgery that had alterations in the arterial gasometry and that required neuromuscular blockade several times during surgery had an increased risk of pulmonary complications. Creagh-Brown et al. [30] evaluated the effect of the peak serum lactate, in the first 24 h of ICU admission after major gastrointestinal surgery, in a large cohort of patients from nearly 250 hospitals in the United Kingdom. In that study, they found an increased in-hospital mortality associated with elevated lactate levels, with no difference between elective and emergency surgery. Veličković et al. showed that lactate levels measured at 12 h after the operation had the highest predictive ability for diagnosis of overall postoperative complications including PPCs and the postoperative in-hospital mortality [31]. Therefore, lactates should be monitored in the immediate postoperative because they help to identify the risk of PPCs.

In our series, patients who required NMBD several times intraoperatively developed a higher rate of PPCs in the first 48 h. Recent studies evaluating the use of neuromuscular blocking agents and postoperative complications have demonstrated growing evidence for a clear relationship between the use of these agents and PPCs complications [32].

It is necessary to underline that the need for invasive mechanical ventilation was understood by us as the extreme consequence of a PPC. As a respiratory support technique it is not, by itself, obviously therapeutic, and may be associated with several complications, namely mechanical ventilation lung injury, usually manifested in the form of barotrauma, volutrauma, atelectrauma, biotrauma and more recently ergotrauma, globally inserted in the new energy concept of mechanical power, which is now thought to be the basis of mechanical ventilation lung injury [33, 34]. The severity of mechanical ventilation lung injury is partly dependent on the duration of the injury, which is why the safety and efficacy binomial are two important factors. However, in our series ventilation was not correlated with 30-day mortality.

Fernandez-Bustamante et al. [7] in a recent report of 1202 patients undergoing non-cardiothoracic surgery under general anesthesia, patients with at least one pulmonary complication had higher rates of mortality, ICU admission, and length of stay, and all patients were ASA PS class 3 or greater. In our series 25 patients (41.7%) were classified ASA PS classes 3 and 4, who were responsible for 10 (16.7%) of the PPCs before 48 h and 15 (25%) of the PPCs after 48 h. As mentioned before, patients with ASA score 4 had less PPCs in the first 48 h since they received preoperative optimization.

The 30-days postoperative mortality was higher in PPCs developed within 48 h (27.8%), therefore these complications revealed a high lethality rate. Patel et al. also showed that 30-day mortality was higher in patients undergoing abdominal surgery with PPCs [4]. Patients with albumin deficiency prior to surgery had a higher risk of death in the first 30 days after surgery. Lunardi A et al. showed that malnutrition is associated with weakness of the expiratory muscles, decreased chest wall expansion and increased incidence of pulmonary complications in patients undergoing elective upper abdominal surgery [35].

This study has limitations regarding the size of the sample. On the other hand, the fact that it includes only patients who required intensive care after abdominal surgery makes it more homogeneous. Taking our results together, we consider that it is necessary to define variables that predict lung complications in the postoperative period and to establish strategies for the mitigation of PPCs after surgery.

Duarte and Machado reviewed the epidemiology, risk factors and prevention of PPCs and concluded that the clinical and social consequences of PPCs are huge and that prevention of its high incidence continues to be a growing challenge focusing on the importance of preventive strategies, which should be systematically applied in order to achieve better results [36].

Major AS is a great stressor to patients and causes large physiological changes, leads to tissue trauma, immobility, psychological distress and reduced quality of life [37, 38].

Physical exercise prehabilitation has been proposed to improve postoperative outcomes in patients undergoing major AS. Several studies have been published in the literature investigating the effect of preoperative exercise training compared with standard care on postoperative outcomes in major AS concluding that the effect is beneficial [39].

The improvement of physical capacity through prehabilitation may facilitate better recovery after surgery and

the current evidence is that prehabilitation protocols and optimization of preoperative care, in particular, respiratory function, may reduce PPCs incidence and mortality [40–42]. In this sense, it is important to study more comprehensive preoperative risk scores such as P-Possum and ACS NSIQ Risk Calculator to better identify risk patients [43–48].

Conclusions

PPCs after abdominal surgery are still a major problem since they have profound effects on outcomes. Our results suggest that programs before surgery, involve preoperative lifestyle changes, such as nutritional supplementation, exercise, stress reduction, and smoking cessation, recently defined as prehabilitation, was an effective strategy in mitigating postoperative complications by decreasing mortality.

Abbreviations

ABG: Arterial Blood Gases; ARDS: Acute Respiratory Distress Syndrome; ARF: Acute Respiratory Failure; ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia; AS: Abdominal Surgery; ASA PS: Anesthesiologists Physical Status; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; EPCO: European Perioperative Clinical Outcome; MV: Mechanical Ventilation; NMBD: Neuromuscular Blocking Drugs; PICU: Polyvalent Intensive Care Unit; POCs: Postoperative Complications; PPCs: Postoperative Pulmonary Complications

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Authors' contributions

AF and LLS were responsible for the primary conception and design of the article with input from co-authors. Initial drafts of the article were prepared by LLS, AF, JR, LA, and CSS. Additions, modifications, and revisions critical for the important intellectual content of the article were performed by LLS, CC, RSC, CSL, PMC, PL, SL, PM, including final approval of the version to be published. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

The ethics committee of the Hospital Garcia de Orta approved the present study. The authors involved agreed to integrate the research.

Consent for publication

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Publisher's Note

3.3 É imperioso um programa de pré-habilitação para doentes cirúrgicos na África Subsaariana

Um relatório recente da revista médica Lancet aponta que pelo menos 4,2 milhões de pessoas em todo o mundo morrem 30 dias após a cirurgia por ano. Metade dessas mortes ocorre em países de baixa e média renda. Esse número de mortes no pós-operatório é responsável por 7,7% de todas as mortes no mundo, tornando-se o terceiro maior contribuinte após as doenças cardíacas e cerebrovasculares. Na África Subsaariana, há uma taxa mais elevada de mortalidade após complicações pós-operatórias em comparação à observada nos países de alta renda. A OMS apresentou planos e instrumentos para ajudar os países a garantir uma cirurgia mais segura. Contudo, a implementação ainda é frágil na maioria dos países africanos. Em geral, as intervenções para melhorar o prognóstico pós-operatório concentram-se na aplicação de medidas intra ou pós-operatórias, que podem ser tardias para doentes de alto risco. Clínicos e investigadores há muito reconhecem a associação entre a baixa capacidade funcional cardiorrespiratória pré-operatória e resultados adversos no pós-operatório, incluindo complicações na recuperação, maior tempo de internamento em unidades de cuidados intensivos, maior tempo de internamento hospitalar e menor qualidade de vida no pós-operatório. As evidências atuais revelam que um programa de otimização médica das doenças crónicas, diminui a taxa de complicações pós-operatórias, o tempo de internamento e a mortalidade. O que é que os países da África Subsaariana podem fazer para garantir uma cirurgia mais segura? Uma parte importante da solução para a redução da morbimortalidade após a cirurgia na África inclui:

1. Identificar doentes cirúrgicos que podem estar em risco de complicações após a cirurgia e fornecer aos profissionais de saúde recursos para tratar precocemente as complicações no pós-operatório.

2. Aumentar a reserva funcional pré-operatória dos doentes cirúrgicos eletivos para melhorar a recuperação após o tratamento cirúrgico. Essa

abordagem é viável, mas os ensaios clínicos são essenciais para identificar as dificuldades e objetivar os seus benefícios.

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Essay

Prehabilitation program for African sub-Saharan surgical patients is an unmet need

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Abstract

Approximately 4.2 million people worldwide die within 30 days of surgery each year. Half of these deaths occur in low- and middle-income countries. Postoperative deaths account for 7.7% of all deaths globally, making it the third-highest contributor to deaths, after heart disease and stroke. In sub-Saharan Africa, there is a higher rate of mortality following postoperative complications compared to high-income countries. The WHO has tools to help countries provide safer surgery. However, implementation remains poor in most African countries. Interventions focused on intraoperative or postoperative measures to improve perioperative prognosis may be too late for high-risk patients. Poor preoperative cardiorespiratory functional capacity, poor management of pre-existing comorbidities and risk factors and no assessment of the patient´s surgical risk is associated with adverse postoperative outcomes, including mortality, complications, slower recovery, longer intensive care stay, extended hospital length of stay and reduced postoperative quality of life. To significantly decrease morbidity and mortality following surgery in Africa, we propose the implementation of a comprehensive preoperative intervention, that must include: i) risk assessment of surgical patients to identify those at greater risk of postoperative complications for elective surgery; ii) increase the preoperative functional reserve of these high-risk patients, to enhance their tolerance to surgical stress and improve postoperative recovery; iii) anticipate postoperative care needs and organize tools, resources and establish simple workflows to manage postoperative complications. We believe this approach is simple, feasible and will significantly reduce postoperative burden for both patients, hospitals and society.

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Essay

An African continental study of 25 low- and middle-income countries was recently published by Biccard BM *et al.* characterizing perioperative outcomes of 11193 surgical patients. The patients were 66.4% women, 87.3% classified with an American Society of Anesthesiologists (ASA) score of I and II, 29.7% undergoing major surgery and 57.1% urgent/emergency surgery [1]. Arterial hypertension (16.3%), diabetes mellitus (6.8%) and HIV positive/AIDS (11%) were the main comorbidities of the operated patients. Non-communicable diseases (NCD) were the most frequent indication for surgical treatment (42.2%), followed by caesarean section (27.3%), trauma (17.8%) and acute infection (12.7%). Despite being younger, presenting a lower risk profile and low complication rates, surgical patients in Africa were twice as likely to die after surgery in comparison to the global average. Indeed, in hospital mortality was 2.1%, with 18% developing postoperative complications (POC) and 9.5% of the patients died following POC [1]. When considering elective surgery (ES) only, mortality occurred in 1% of 4658 patients, with an incidence of postoperative complications of 13.4% and death after POC of 4.8%.

A greater incidence of POC and death were reported following surgery for NCD (37.3% and 40.3%, respectively), infection (20.2% and 26.5%, respectively) and trauma (20.5% and 25.5%, respectively). Infectious, cardiovascular and respiratory complications were the most prevalent [1]. The factors contributing to POC and death are multifactorial and may include insufficient medical staff, poor infrastructure, low procedural volumes and failure to identify and/or treat POC by health professionals [2,3]. Intensive care admission should also be scheduled in advance. In their study, Biccard BM *et al.* [1] identified that only 16.3% of patients who developed POC, the vast majority after ES, were admitted to intensive care units (ICU) to prevent and treat early complications. The lack of immediate postoperative surveillance and intervention is responsible for many deaths in many African countries. Therefore, acute care surgery (ACS) services should be implemented even in a low-resource setting [4].

In Rwanda, the implementation of an ACS service resulted in decreased length of hospital stay [5]. Thus, while surgical care is a major need for African countries, surgical outcomes will remain poor unless effective perioperative care based on affordable resources is made universally available. Perioperative care is a multicomponent intervention implemented by a multidisciplinary team with the purpose to provide safe surgery, accelerate recovery and reduce morbidity and mortality (Figure 1). While the intra- and postoperative care have already received some attention, the potential of the perioperative period remains poorly explored in African countries [6-11]. This time frame represents a major opportunity for decreasing postoperative morbidity and mortality through appropriate surgical risk stratification and patient optimization [12].

Risk assessment of surgical complications in sub-Saharan Africa: in an environment with limited resources for postoperative care, the early identification of high-risk patients for POC is likely to be a key factor to consider. Several tools are available to estimate perioperative risk for both planned and emergency surgeries in high-income countries [13,14]. However, their use in low-income countries is often limited because the pattern of risk for poor outcomes differs from high-income countries and due to the lack of resources, the access to biochemical and imagological tests required by more sophisticated tools is reduced [15]. Recently, Kluyts H-L *et al.* proposed the use of the ASOS surgical risk calculator as a simple tool to identify African surgical patients at risk for in-hospital postoperative mortality and severe complications and thus, to identify those patients in greater need for enhanced postoperative surveillance [16]. However, its external validation needs to be assessed before. To predict complications and risk of death before surgery, other African authors have conducted relevant studies, including the use of online tools, provided that this tool has wide distribution [17,18]. This is a field that deserves further research effort as it may greatly contribute to save lives.

Estimating the risk of complications and mortality of surgical patients before surgery can be helpful: risk stratification of patients is supposed to support better decisions by informing about the risks and benefits of proceeding with surgery, about discussing treatment alternatives and guide the use of available resources, with the ultimate purpose of improving postoperative outcomes. Ntobeko Ntusi, a South African cardiologist, in a recent editorial in the South African Medical Journal, asked: "does the preoperative evaluation of patients improves surgical outcomes?". He found that the data on the effect of preoperative medical consultation on cost measures is conflicting [19]. While some studies reveal a decrease in-hospital stay after preoperative evaluation and care of patients [20,21], other studies have shown an increase in costs and a similar length of stay for consulted patients [22-24]. He also points that while medical teams can successfully identify conditions that may affect surgical outcomes, it is not clear if they make evidence-based recommendations to target

those conditions and assuming they make it, it is also not clear if the consultative recommendations are implemented [19]. With this data and his experience, Ntusi argued that an experienced perioperative medicine physician should be able to identify the pertinent medical problems, anticipate potential perioperative problems, recommend evidence-based interventions to optimize the patient and communicate and work effectively with all the preoperative team members (e.g. nursing, physiotherapist, medical, surgical and anesthetic) [19]. Thus, to deal with the problem of postoperative morbidity and mortality, the perioperative care, particularly the potential of the pre-surgical period to optimize the patient for surgery, needs to be taken more seriously. These patients need and deserve better care and prehabilitation programs can make the difference once incorporated in the routine practice of surgical teams.

Prehabilitation to prepare for surgery: the impact of surgery leads to significant homeostatic disturbance which, together with reduced functional capacity (physical, nutritional and psychological status) and poor medical optimization (e.g. unappropriated management of chronic diseases, anemia, hypertension, hyperglycemia and smoking), act as risk factors for negative surgical outcomes [25]. Prehabilitation is a multimodal strategy implemented in the preoperative period, aiming to increase preoperative functional reserve and leading to better postoperative functional recovery and reduced incidence of complications. In practice, prehabilitation programs may include cardiovascular and resistance training exercises, nutritional advice designed to support an increase in lean body mass, the introduction of coping strategies to deal with surgical anxiety, smoke cessation support, treating preoperative anemia and other modifiable risk factors [26]. An increasing number of studies support the safety, feasibility and efficacy of multimodal prehabilitation to improve surgical outcomes in cancer patients undergoing major abdominal and cardiothoracic surgery [27]. The benefits range from lower rate of postoperative complications, to less deterioration of physical function and better quality of life [28]. However, this evidence comes mainly from high-income countries and thus, there is an urgent need to test the potential of prehabilitation programs in African countries.

Conclusion

Decreasing morbidity and mortality following surgery in Africa will require adequate perioperative optimization and better postoperative care planning. Preoperative diagnosis of comorbidities and social habits that are considered risk conditions for surgery should be identified throughout appropriate risk assessment tools. Patients considered to be at high-risk for complications following surgery should be proposed for prehabilitation to increase their preoperative functional reserve and enhance recovery following surgical treatment. The knowledge about most common surgical complications should be used to anticipate postoperative burden, care needs and organize available resources in advance. We believe that this approach to perioperative care will play a decisive role in sub-Saharan Africa in changing surgical morbidity and mortality for better.

Competing interests

The authors declare no competing interests.

Authors' contributions

AVF and LLS were responsible for the primary conception and design of the article with input from co-authors; AVF, DMG and LLS prepared initial drafts of the article. Additions, modifications and critical revisions for the relevant intellectual content of the report were performed by AVF, DMG, JC, NCR, VC, LVL, PMC and LLS, including final approval of the version to be published. All the authors have read and agreed to the final manuscript.

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Figure

Figure 1: stratification of measures to decrease perioperative morbidity and mortality in surgical patients

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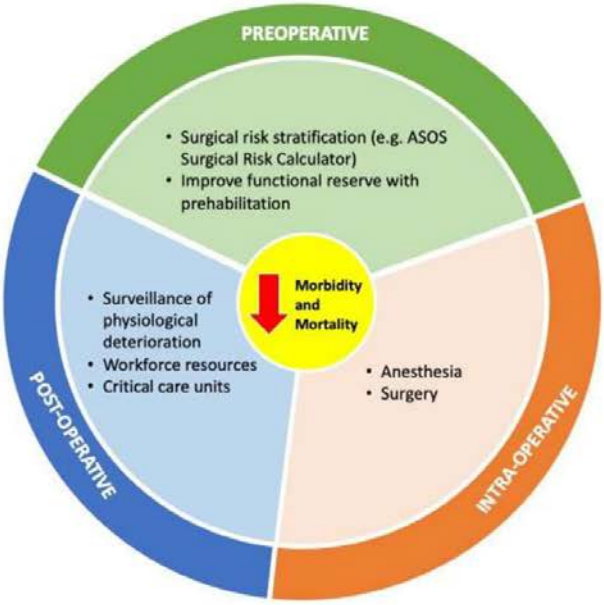

Figure 1: stratification of measures to decrease perioperative morbidity and mortality in surgical patients

3.4 Um programa de pré-habilitação domiciliar, implementado através de uma plataforma digital, em doentes com adenocarcinoma gástrico ou junção gastoesofágica localmente avançado, submetidos a quimioterapia perioperatória com regime FLOT: protocolo de um estudo multicêntrico, randomizado, controlado para avaliar a viabilidade e aceitação.

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Importância: A quimioterapia perioperatória é a abordagem de tratamento padrão para doentes com adenocarcinoma gástrico ou esofágico localmente avançado. Apesar dos ganhos de sobrevida, esta terapia multimodal não é isenta de efeitos adversos, colocando uma proporção significativa de doentes em risco de morbimortalidade pós-operatória.

Objetivo: Testar a aceitação, viabilidade e segurança de um programa de pré-reabilitação domiciliar, implementado por meio de uma plataforma baseada na Internet, em doentes submetidos a quimioterapia neoadjuvante (QNA) e ressecção cirúrgica para adenocarcinoma gástrico ou junção gastroesofágica (JGE).

Métodos: Realizaremos um estudo multicêntrico, simples-cego, de dois braços, randomizado e controlado com proporção de alocação de 1: 1, comparando o programa de pré-habilitação domiciliar com o atendimento padrão. Doentes com adenocarcinoma gástrico ou JGE localmente avançado, potencialmente ressecável, submetidos a quimioterapia perioperatória com regime FLOT serão recrutados no IPO-Porto e randomizados (proporção de 1: 1) para grupo controlo (CONT; cuidado usual com otimização médica, atendimento nutricional e psicológico) ou grupo de pré-habilitação (PREHAB, cuidados usuais + programa de exercício físico no domicílio). A intervenção com exercício incluirá treino

aeróbico e resistido. Todos os participantes serão submetidos a avaliações no início do estudo, após a QNA, antes da cirurgia e no momento da alta.

Resultado: O principal resultado deste estudo é testar a aceitação, viabilidade e segurança da intervenção. Como objetivos secundários, pretendemos avaliar o impacto da pré-reabilitação domiciliar na capacidade funcional, severidade da fragilidade, tolerância e eficácia do FLOT, qualidade de vida, incapacidade, complicações pós-operatórias e mortalidade, tempo de internamento hospitalar, necessidade de UCI, readmissão hospitalar e local após a alta.

Discussão: Este estudo fornecerá informações para realizar um futuro ensaio clínico multicêntrico randomizado com o objetivo de reduzir a morbidade e mortalidade pós-operatória nesta população.

Title: A home-based prehabilitation program, delivered through an internet-based platform, in patients with locally advanced gastric or oesophagal adenocarcinoma, undergoing perioperative chemotherapy with FLOT regimen: protocol for a feasibility and acceptability study of a multicentric, randomized, control trial

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ABSTRACT

Introduction: Perioperative chemotherapy is the gold standard treatment approach for patients with locally advanced gastric or oesophagal adenocarcinoma. Despite the gains in survival, this multimodal therapy is not free of adverse effects, putting a significant proportion of patients at risk for postoperative morbidity and mortality. The purpose of this study is to test the acceptability, feasibility and safety of a home-based prehabilitation program, delivered through an internet-based platform, in patients undergoing neoadjuvant chemotherapy (NAC) and surgical resection for gastric or oesophagal adenocarcinoma. Methods: We will conduct a multicenter, single-blinded, two-arm, randomized controlled trial with 1:1 allocation ration, comparing home-based prehabilitation program versus standard care. Patients with locally advanced, potentially resectable gastric or GEJ adenocarcinoma, undergoing perioperative chemotherapy with FLOT regimen will be recruited at IPO-Porto and randomized (1:1 ratio) to control (CONT; usual care with medical optimization, nutritional and psychological care) or prehabilitation (PREHAB, usual care+home-based exercise training program) groups. Exercise intervention will comprise aerobic and resistance training. All participants will undergo assessments at baseline, after NAC, before surgery and at time of discharge. The primary outcome of this study is to test the acceptability, feasibility and safety of the intervention. As secondary outcomes, we intend to assess the impact of home-based prehabilitation on functional capacity, frailty status,

tolerance and efficacy of FLOT, quality of life, disability, postoperative complications and mortality, length of hospital stay, need of ICU, hospital readmission and place for discharge. Discussion: This trial will inform about a future multicentre randomized clinical trial to reduce post-operative morbidity and mortality in this population.

1. INTRODUCTION

1.1. Background and rationale

Adenocarcinoma of the gastroesophageal junction (GEJ) and stomach are among the most common malignancies and causes of cancer death worldwide, including Portugal which has one of the highest incidence rates in Europe, predominantly occurring in patients > 65 years of age [1]. In patients with locally advanced disease, perioperative chemotherapy (PCT) is considered standard of care, as different clinical trials demonstrated its superiority in improving survival when compared to surgery alone [2]. However, this multimodal therapy is not free of adverse effects. PCT promotes significant deconditioning and physiological deterioration [2], impacting the patient's tolerance to surgery, which puts them at higher risk for postoperative morbidity and mortality [3]. Even with the most recent PCT regimes, around 50-60% of patients develop postoperative complications [2], with pulmonary complications on the top of the list. Postoperative complications can impose a significant burden by increasing morbidity and mortality, in-hospital length of stay, utilization of critical care and need for a greater level of care at discharge [4, 5]. Moreover, postoperative complications may prevent or cause delays in the administration of adjuvant chemotherapy, which is associated with worse disease-free and overall survival [6]. Given the growing incidence of proximal gastric cancer and GEJ tumours and because these patients often present with age-related functional decline, comorbidities and geriatric syndromes (e.g. frailty), these patients are at greater risk for adverse postoperative outcomes [7]. Presumed fear of more significant postoperative morbidity and mortality often results in suboptimal delivery of cancer surgery, which is the most efficient curative approach for solid tumours. Thus, it is mandatory to invest in strategies capable of minimizing the adverse effects of PCT and surgery by boosting the patient's physiological reserve.

Interventions to improve postoperative outcomes have usually been intra- and postoperative, which might be too late for these high-risk patients. The preoperative period is now regarded as an excellent window of opportunity to optimize patients by intervening with factors known to contribute to postoperative outcomes. The process of enhancing the functional capacity to cope with an incoming stressor and optimize recovery has been termed prehabilitation [8]. A growing body of evidence supports the role of prehabilitation to improve postoperative outcomes such as physical fitness, quality of life, the incidence of postoperative complications and length of hospital stay in cancer patients submitted to significant surgery [9-11]. However, existing studies show a clear bias towards certain types of cancers (oesophagal, colorectal, lung) and are underpowered to address significant outcomes like postoperative complications. Moreover, the effectiveness of prehabilitation in high-risk patients for postoperative complications remains discussed poorly, and these are the patients who are in greater need of better care. Besides, the majority of the prehabilitation programs are developed under supervision in an outpatient clinic, which might be an obstacle for those patients with geographical and/or travelling constraints [12]. Community-based programs, with the support of telehealth resources, were already shown to be a convenient way to surpass these barriers and provide safe and effective cardiac rehabilitation care [13]. Using this approach to deliver prehabilitation could be very useful to prepare cancer patients at higher risk for postoperative burden.

1.2. Objetives

The primary outcome of this study is to test the acceptability, feasibility and safety of a home-based prehabilitation program, delivered through an internet-based platform, in patients with locally advanced gastric or oesophagal adenocarcinoma, undergoing perioperative chemotherapy with FLOT regimen.

As secondary outcomes, we intend to assess the impact of home-based prehabilitation on functional capacity, frailty status, tolerance and efficacy of FLOT, surgical stress, quality of life, disability, postoperative complications and mortality, length of hospital stay, need of ICU, hospital readmission and place for discharge. This trial will inform about a future multicentre randomized clinical trial to reduce postoperative morbidity and mortality in this population.

1.3. Trial design

This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [14]. We will conduct a multicenter, single-blinded, two-arm, randomized controlled trial with 1:1 allocation ration, comparing home-based prehabilitation program versus standard care. Patient recruitment is programmed to start in October 2020 until April 2021.

2. METHODS

2.1. Study setting and design

The study will be conducted in two Portuguese tertiary centres (Instituto Português de Oncologia do Porto Francisco Gentil, E.P.E, Porto (IPO-Porto) and Hospital Garcia de Orta, Lisbon (HGO-Lisbon)). All the assessments will take place in the aforementioned hospitals, and the intervention will be home-based. An overview of the study design is shown in a schematic diagram (Figure 1).

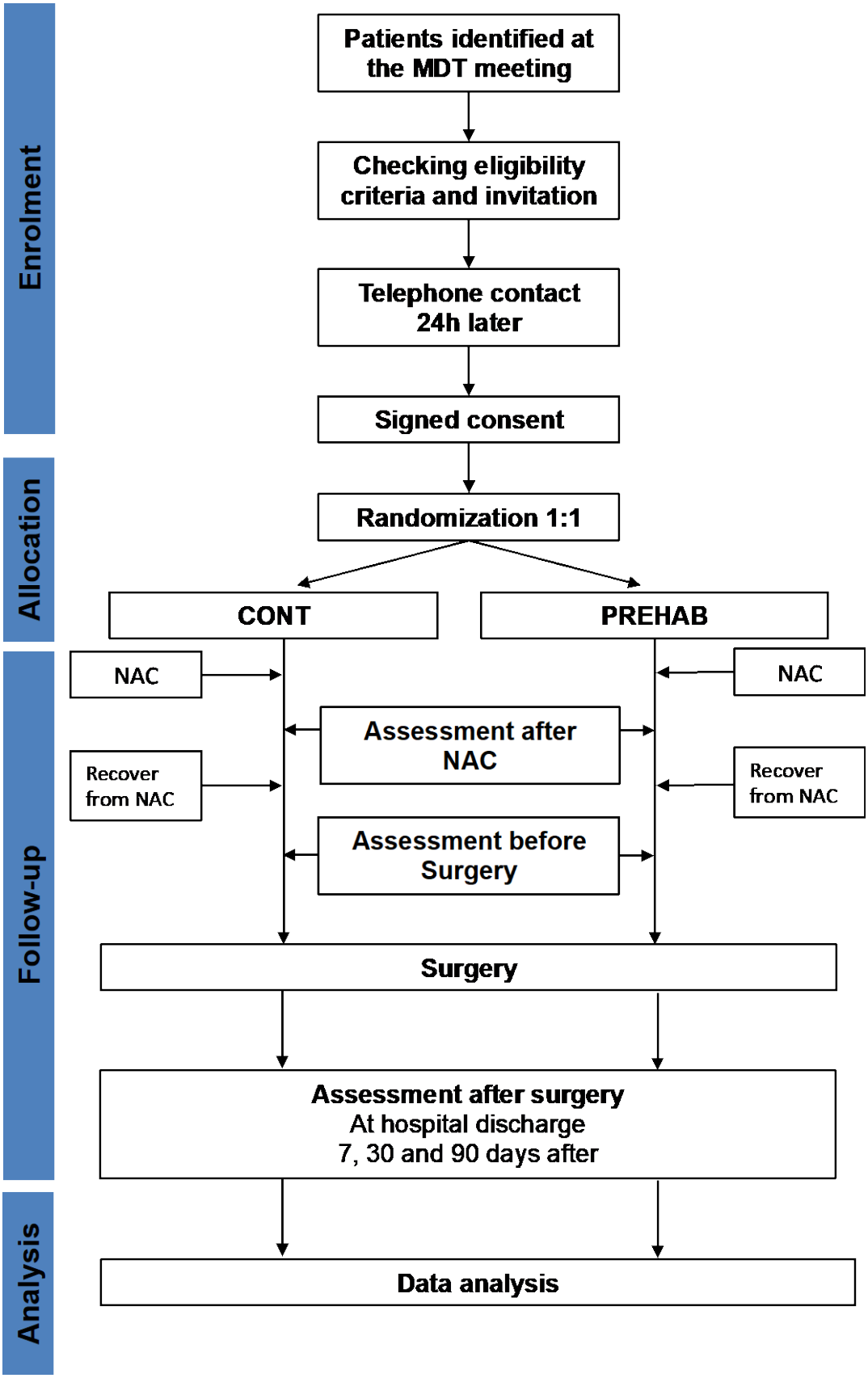

Figure 1: Consort diagram of the study

2.2. Recruitment

Potential participants will be identified at the multidisciplinary oncology meeting, where the management plan of the patient is decided. All consecutive patients with locally advanced, potentially resectable adenocarcinoma of the stomach or GEJ junction undergoing perioperative chemotherapy with FLOT regimen will be signaled. In the first clinic visit to discuss the therapeutic plan, a surgeon or medical oncologist, or anesthesiologist will screen for eligibility and ask the patient to consider participating in the trial. Patients will receive a handout detailing the rationale of the study, what participation will implicate obligations and possible risks. After 24 hours, a team member will contact patients by phone to clarify any issue related to the trial and to schedule the first research visit to complete the enrolment for those willing to voluntarily participate.

During the first research visit, participants will sign the consent form and only consenting patients will proceed to further evaluations. Participants will also be informed that they may discontinue and/or withdrawal the trial at any time without compromising their standard care. The investigator or the medical team may stop a participant from the test due to the following reasons, but not limited to: i) withdrawal of consent; ii) not compliant with study arm and procedures; iii) development of a new medical illness restrict the participation in physical exercise; v) adverse events considered incompatible with the safe continuation in the trial; vi) the investigator and/or the medical team decide it is for the best interest of the patient. The reasons for the participant's withdrawal and/or discontinuation from the trial will be recorded.

2.3. Eligibility criteria

We will include consecutive patients with locally advanced, potentially resectable adenocarcinoma of the stomach or GEJ junction undergoing perioperative chemotherapy with FLOT regimen that fulfil the following criteria: i) >18 years old ii) with no contraindications for physical exercise [15]; iii) returning signed informed consent; iv) accepting to comply with the trial procedures.

Patient treated for another cancer within five years (except basal cell skin carcinoma or carcinoma in situ of the cervix), with legal incapacity (person

deprived of liberty or under guardianship), cognitive or severe psychiatric disorders, breastfeeding, pregnancy (or planning to become pregnant) will be excluded.

2.4. Randomization and group allocation

Eligible patients will be randomized using computer-generated blocks of 4, with an online tool (Sealed Envelope Ltd. 2019. Create a blocked randomization list. [Online] Available from https://www.sealedenvelope.com/simple-randomiser/v1/lists) and sequentially allocated in a 1:1 ratio to either prehabilitation (PREHAB) or a control (CONT) group. A designated staff member, with no involvement on trial, will carry out the randomization.

2.5. Intervention

2.5.1. CONT group

Participants assigned to the CONT group will receive standard care, which includes medical optimization (ex: control of risk factor and chronic diseases), nutritional and psychological care (in case of need). A clinical nutritionist evaluates the need of nutritional care through the Patient Generated Subjective Global Assessment (PG-SGA), where and a score ≥9 indicates a critical need for nutrition intervention [16]. An individualized plan in then offer to the patient, which may include suggestions of meals and a list of foods to avoid/to favor, to help to obtain the recommended amount of protein intake (1.2-1.5 g/kg/d) [17]. A clinical psychologist evaluates the need of psychological care with the NCCN Distress Thermometer and Problem List (DTPL) (Version 2.2020). Patients indicate their level of distress over the course of the week prior to assessment. In those patients reporting high levels of distress (score >4), the accompanying 40-item problem list, detailing common problems related to the cancer experience, will be reviewed and a personalized intervention is developed. This may include training on strategies to cope with stress and anxiety, relaxation exercises and good sleep hygiene, as needed. Patients also receive general instructions about the importance of remaining physically active during treatment as part of the standard

care, but no formal exercise prescription is provided. Patients will be asked to record their activity on a logbook.

2.5.2. PREHAB group

Patients allocated to the PREHAB group will have usual care plus a specific exercise training program to be performed at home. The intervention will start as soon as possible after treatment decision and will be interrupted at time of hospital admission for surgery (±15 weeks). We will use multimodal prehabilitation, which means combining exercise interventions with nutritional and psychological care, on top of medical optimization. Since medical optimization, nutritional and psychological care are already part of usual care, a structured exercise program will be added.

The exercise training program will consist of combined exercise training (aerobic exercise plus resistance exercise) and inspiratory muscle exercises, which was shown to be safe and effective to improve functional capacity in patients during chemotherapy [11]. A baseline fitness assessment will inform about the participant's fitness level and assist the tailoring of the exercise program, objectives and progression. Participants will be invited to perform, as tolerated, three sessions per week of combined exercise. For aerobic exercise (AEx), participants may opt for walking, jogging or cycling. After warming up for 5 minutes at their perceived exercise intensity of "light" (9-11 Borg' scale), patients will be asked to engage on 30 min of Aex at "moderate" intensity (12-13 Borg' scale). The intensity and/or duration level will be adjusted through the intervention, if necessary. After Aex, the participant will be asked to start 1 set of 8 to 15 repetitions of the following exercises: i) chair squats (modified to the individual's level of function as squats); ii) wall press iii) seated row with resistance bands; iv) chair dips; v) bicep curls with resistance bands; vi) abdominal crunches (modified to be performed sitting in a chair). When a participant completes the 15 repetitions before the point of muscle fatigue, the progressive addition of sets of exercises will be asked, as tolerated. This will take 10-15 minutes. At the end of each exercise session, participants will be asked to perform some stretch exercises. PREHAB patients will be recommended to walk in the remaining days (except on days of prescribed training sessions), for >30 minutes/day at moderate intensity. If the participant has a poor baseline

conditioning, the day after their exercise session will be used to rest and allow recovery. As their fitness improves, rest days will be replaced by walking.

In order to deliver and monitor our home-based prehabilitation, participants will be assigned with individual credentials to access an internet-based platform (therapy) via computer or mobile devices. Therapy is a responsive and customizable platform, with an embedded data collection system (e.g. Participants reported outcomes, questionnaires, etc.), that allows delivery of different treatment modalities (text, graphical content and video) and access to an end-to-end encrypted internal communication system (e-mail, chat and videoconference) [18]. This platform is currently being used by our team members to deliver a psychosocial intervention targeting breast cancer survivors [19]. Therapy features will be used throughout the intervention to i) provide the tailored prehabilitation intervention (information about exercise prescription, instructions and videos exemplifying the exercises and with verbal explanations of most important aspects to consider); ii) facilitate bi-directional communication in case of need; iiI) measure the compliance and adherence to the program; iv) obtain information about the weekly progress and adjust the intervention; v) assess/report the occurrence of any adverse events; vi) clarify any issue and reinforce the importance of maintaining the prescribed program. For patients unable to use therapy, a book with instructions and cartoons exemplifying the exercises will be provided, followed by a particular explanation and demonstration. A member of the trial team (ideally a physiotherapist or exercise physiologist) will contact each participant by telephone weekly to collect compliance and adherence metrics.

2.6. Assessments

2.6.1. Demographic and clinical data

Baseline demographic, clinical characteristics and physical activity levels of consented patients will be captured at the moment of their initial assessment during the first research visit. Clinical files might also be used to complete and confirm the patient's profile. The following information will be recorded: age, gender, marital status anthropometry, risk factors, chronic drug therapy, type and complexity of the surgery, the surgical risk with standard tools (e.g. ASA score,

ECOG, P-POSSUM, Charlson Comorbidity Index) and with the MyIPOscore [20]. MyIPOscore is a tool developed by us and is currently being prospectively validated at our institution. This stratification will not affect clinical decision but will be used for subanalysis to compare outcomes between high and low-risk patients. Clinical files might also be used to complete or confirm the patient's profile.

2.6.2. Outcome measurements

Table 1: Provides a timeline of assessments of the outcome measures

Outcomes	Assessment measure	Baseline	Intervention		Before surgery	Surgery	After surgery			
			During NAC	After NAC			7 days	30 days	90 days	Discharge
Primary outcomes										
Feasibility	Willingness of clinicians to recruit participants	x								
Feasibility Acceptability	Willingness of patients to be randomized	x								
	Recruitment rate	x								
	Eligibility rate	x								
	Adherence rate		x	x						
	Number of patients declining to participate	x								
Safety	Number and severity of adverse events		x	x						
Secondary outcomes										
Morphometry	Weight	x		x	x					
Morphometry Body composition	Height	x		x	x					x
	BMI	x		x	x					x
	Bioimpedance	x		x	x					x
Physical activity levels	Accelerometer	x		x	x					x
Physical fitness	6MWD	x		x	x					x
Physical fitness Frailty status	30-second chair stand	x		x	x					x
	30-s arm curl	x		x	x					x
	Chair sit-and-reach	x		x	x					x
	Back scratch	x		x	x					x

	8-foot up-and-go	x		x	x					x
	Fried's frailty phenotype	x		x	x					x
HRQoL	EORTC QLQ-C30, version 3	x		x	x					x
Tolerance to NAC	Dose		x							x
Tolerance to NAC Eficacy of NAC	Adverse effects		x							
	Completion rates		x							
	Reduction of tumor size, number and size of lymph nodes measured by endoscopic ultrasound (EUS) or CT-Scan	x			x					
Eficacy of NAC Disability	R0-resection rate					x				
	Pathologic complete response (pCR) rate					x				
	Histologic tumor regression grade					x				
	WHO Disability Assessment Schedule V.2.0	x		x	x					
Morbidity	Postoperative Morbidity Survey						x			x
Morbidity Mortality	Clavien-Dindo						x	x	x	
	Comprehensive Complication Index						x	x	x	
	Death from any cause					x	x	x	x	
Health-care resources	In-hospital length of stay							x	x	
Health-care resources	Need of intensive care						X			X
	Readmissions						X	X	X	
	Place for discharge							X	X	

2.6.2.1. Primary outcomes

2.6.2.1.1. Feasibility

The feasibility of the intervention will be measured by i) assessing the willingness of clinicians to recruit participants, ii) willingness of patients to be randomized, iii) recruitment rate (number of patients recruited per month), iv) eligibility rate (number of patients fulfilling inclusion criteria per month), iv) retention (participants retained and assessed in the follow-up period), v) adherence rate to the prehabilitation program (the degree to which patients correctly follow prescription instructions) and vi) the generalizability of trial participants (comparing their demographic and clinical features with all other patients submitted to surgery). Data will be collected during the entire period of the trial.

2.6.2.1.2. Acceptability

Acceptability of the intervention will be measured by assessing the number of patients declining to participate in the trial. Reasons for non-participation will be recorded.

2.6.2.1.3. Safety

The safety profile of the intervention will be assessed by measuring the number and severity of adverse events occurring during the exercise training sessions. The reporting period will be during the prehabilitation program. In the unlikely possibility of happening, AE may be spontaneously reported by the participants or recorded by the trial team members during the weekly follow-up phone calls.

2.6.2.2. Secondary outcomes

2.6.2.2.1. Tolerance and efficacy to chemotherapy

Patients will receive six cycles of neoadjuvant FLOT consisting of 5-FU 2600 mg/m2 (24-hr infusion), leucovorin 200 mg/m2 (1-hr infusion), oxaliplatin 85 mg/m2 (2-hr infusion), docetaxel 50 mg/m2 (1-hr infusion) repeated every two weeks. Information about the dose, adverse effects, and completion rates (dividing the dose of chemotherapy per square meter in each cycle by the number

of weeks in a cycle) will be extracted from the medical records. A chemotherapy completer will be defined as having received dose intensity of 100%, while someone below 100% will be considered a non-completer. To evaluate the impact of the intervention in response to chemotherapy, we will assess reduction of tumour size, number and size of lymph nodes measured by endoscopic ultrasound (EUS) or CT-Scan before and after NACT termination. Because these patients will then proceed to surgery, we will also compare R0-resection rate, pathologic complete response (pCR) rate (defined as T0N0) and histologic tumour regression grade (TRG) between PREAHB and CONT group, obtained from surgical and pathological reports.

2.6.2.2.2. Physical and functional assessments

These assessments will be made at four time-points: i) before starting chemotherapy (define baseline level), ii) after chemotherapy and iii) before surgery (comparison with baseline levels and test if the program mitigates functional decline), and iv) time of discharge (compare with previous levels and correlate with clinical outcome measures). It will include measuring morphometry (weight, height and BMI), body composition (bioimpedance), physical activity levels, physical fitness and frailty status. The Senior Fitness Test measures basic mobility-related parameters: aerobic endurance (6 min walking distance test, 6MWD), lower and upper body strength (30-second chair stand and 30-s arm curl, respectively), lower and upper body flexibility (chair sit-and-reach and back scratch, respectively), and agility/dynamic balance (8-foot up-and-go). This is a valid instrument that provides fitness standards (performance cut points) to identify individuals at greater risk of premature loss of mobility and independence [21, 22]. Moreover, the performance at the 6MWD was previously shown to be independently predictive of post-operative complications and recovery in cancer patients [23-25]. Regarding frailty status, in the absence of a well-accepted gold standard tool to assess frailty, we will use the phenotype model proposed by Fried [26]. Fried's frailty phenotype considers the analysis of five physical health items: unintentional weight loss; exhaustion; low energy expenditure (or inactivity status); slowness; and weakness. Deterioration of each of these domains is scored as one if present or 0 if absent, giving a potential score spanning from 0 to 5. Ultimately, three phonotypical categories will be obtained: fit (no

deterioration); prefrail (one or two items); or frail (three or more things). Multiple epidemiological studies have found that frailty diagnosis with this tool was predictive of postoperative complications and mortality in older surgical patients [27, 28].

2.6.2.2.3. Patient-reported outcomes

Patient-reported outcomes will be measured in the same four time-points previously defined for functional capacity. Health-related quality of life will be assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30, version 3). The EORTC QLQ-C30 is a reliable and valid measure of the perceived health-related quality of life of patients diagnosed with cancer in the multicultural clinical research setting [29]. Patent-reported disability will be measured using WHO Disability Assessment Schedule V.2.0, which is a questionnaire that assesses activity limitations and participation restrictions (i.e. disability) in the prior month [30]. It covers six domains of functioning, including 1) understanding and communication; 2) self-care; 3) mobility (getting around); 4) interpersonal relationships (getting along with others); 5) work and household roles (life activities); and 6) community and civic roles (participation). This tool was validated in a variety of disease states, including surgery [31], and was found to be as responsive to change as disorder-specific functional measures [32].

2.6.2.2.4. Postoperative burden

These outcomes will be measured at 7, 30 and 90 days postsurgery. Data will be collected by an outcome assessor blinded to the intervention and with no role in any other part of the trial or in the patient's clinical care pathway. Data will be retrieved from the hospital clinical information system as well as from the patient's files, clinical notes and caregivers. If needed, the discharged patient will be contacted by telephone and interviewed around day 90 after surgery. The Postoperative Morbidity Survey (POMS) will be used to describe postoperative morbidity [33]. The POMS contain 18 items that address nine domains of postoperative morbidity (pulmonary, infectious, renal gastrointestinal, cardiovascular, neurological, haematological, wound and pain). For each part, either presence or absence of morbidity is recorded on the basis of objective

criteria. The severity of the complications will be graded by using the Clavien-Dindo classification system [34] and the Comprehensive Complication Index [35]. The outcome assessor will record the number of events per participants as well as the number of participants with a complication. Death from any cause will be recorded until day 90 after surgery. Health-care resource utilization will be assessed by measuring the in-hospital length of stay (number of days in hospital after the surgery, with the day of surgery counting as day 0), need of intensive care (number of days in intensive care unit), readmissions (number of hospital admittance after discharge, with the day of discharge counting as 0) and place for release after leaving the hospital (institution versus home).

2.7. Data collection, management and monitoring

Patients will be informed and explicitly authorize the collection, storage and use of data for the research purpose in the signed consent form.

Data will be collected from clinical records and database systems at the hospital or assessed with the patients (e.g. questionnaires and physical fitness). All documents will be stored securely in confidential conditions where only the principal investigator has key access. In all other project-specific documents (including any database), other than the signed consent, the participant will be referred by the trial participant number and subject number (if applicable), not the name. Tissue samples collected as part of routine care according to procedures of standard clinical practice implemented at participating institutions will be coded in collaboration with the Clinical Pathology Department, and only then provided to team members. A cloud-based platform (Azure) will be designed and open to all project members, to centralize data into a repository. Security and privacy will be granted according to The European Union General Data Protection Regulation (approved by the European Parliament in 14/4/2016; Enforcement date: 25/5/2018). The trial data will be regularly monitored and audited at regular intervals by the local clinical trials department and Experimental Pathology and Therapeutics Group.

2.8. Blinding

Participants will be informed that they are being enrolled in a study that aims to assess the relationship between their presurgical physical activity levels and their postoperative outcomes and thus, will not be blinded to the intervention. To avoid bias, care providers and outcome assessors will be blinded to the participation in the clinical trial. Data analysts will also be blinded to the treatment allocation. Only those directly involved with the management of the intervention will not be overwhelmed. Unblinding will be permissible in case it is essential for the participant's standard care. The request needs to be submitted to the chief investigator, who will decide if revealing the allocation status will influence the continuity of the participant in the trial.

2.9. Ethics and dissemination

The project will be conducted in accordance with the Declaration of Helsinki and National Legislation. Team members are committed to working according to the Good Clinical Practices, in agreement with the Declaration of Helsinki and respecting patients' confidentiality. The local Ethical Authorities already approved the study protocol and informed consent (supplement).

Adverse events caused by prehabilitation exercises are rare and of minor impact [11]. We will minimize this by screening the patients for the presence of absolute and relative contraindications to exercise [15] and by following the exercise guidelines for cancer patients [36]. Participants will be submitted to the standard procedures related to their treatment plan, decided at the multidisciplinary oncology meeting, as usual. Thus, participants in the study will have the risks associated with the procedures they usually are submitted (e.g. collection of blood and urine samples, imaging for disease staging, adverse effects of chemotherapy and surgery), which excludes the need for additional trial insurances.

Research findings will be disseminated through peer-reviewed journals with impact to the scientific community, and public presentations (to clinicians, to academic audiences, and in national and international meetings). Data produced will be made available to the scientific community and the society according to

the ethical and social rules of involved institutions and government. The laws on open access publications (Green or Gold) will have complied. All academic journals (e.g. final articles or manuscripts accepted for publication, thesis) will be deposited into the institutional repository of the involved research institutions respecting the embargo period.

2.10. Statistics

No sample size calculation was preestablished as we are primarily interested in precise estimates of feasibility and acceptability, as well as outcome variability that will aid in the planning of a larger, sufficiently powered efficacy trial to compare the effectiveness of prehabilitation to reduce postoperative morbidity and mortality in patients elected for surgery. This exploratory pilot study will enable us to collect the preliminary data we require to perform an accurate sample size calculation for the full review.

The analysis will be conducted with SPSS, version 28 (IBM Corp., USA). Normality of data will be determined by using the Shapiro-Wilk test. Baseline features will be described as mean±SD or median (interquartile range) for continuous data and as frequency and percentage for categorical data. Comparison between independent groups will be analyzed using Student t-test or Mann-Whitney's test for continuous variables or Chi-squared or Fisher's exact test for categorical variables.

Statistical comparisons of secondary outcomes across the intervention and control arms will be performed for patient demographics (age, frailty, physical fitness, surgical risk score), duration of surgery, site of surgery (upper vs lower abdominal), use of regional anaesthesia and blood product utilization. If there are differences between the intervention and control arms, multivariate models will be performed to adjust for these baseline differences. A two-sided p-value <0.05 will be considered to indicate statistical significance.

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Capítulo IV - DISCUSSÃO, CONCLUSÕES E TRABALHOS FUTUROS

Neste capítulo fazemos a discussão global e integrada dos nossos resultados apresentando as principais conclusões dos nossos trabalhos, salientando a potencialidade do emprego do MyIPOrisk-score como instrumento de avaliação do risco pré-operatório em cirurgia oncológica digestiva. De igual modo expomos e discutimos algumas das possibilidades de desenvolvimentos futuros deste trabalho.

4.1 Instrumentos de avaliação de risco cirúrgico na predição de complicações pós-operatórias em doentes do foro de oncologia digestiva

O doente oncológico apresenta um risco elevado de CPO quando submetido à cirurgia do trato gastrointestinal, às quais se associa uma taxa de morbilidade e mortalidade importante, particularmente naqueles que apresentam, concomitantemente, comorbilidades e síndromes geriátricos [1-5]. Com o intuito de prever a morbilidade e a mortalidade associada a uma determinada intervenção cirúrgica, a cirurgia oncológica utiliza instrumentos de avaliação de risco cirúrgico, tendo em conta a complexidade clínica e anátomo-cirúrgica de cada doente [6, 7]. O conhecimento do risco no período pré-operatório tem como finalidade auxiliar a decisão médica sobre a elegibilidade do doente para o tratamento cirúrgico e/ou orientar sobre a necessidade de instituir um programa de otimização pré-cirúrgico com o intuito de aumentar a tolerância para o stress cirúrgico e mitigar os seus efeitos adversos [8-12]. No entanto, como revisto previamente (Capítulo I) são cada vez mais os estudos que alertam para a baixa validade externa destes instrumentos na população cirúrgica em geral. Adicionalmente, são também cada vez mais abundantes os estudos que

reconhecem a falta de concordância entre diferentes instrumentos (apesar amplamente utilizados a nível global) que avaliam o mesmo indicador de prognóstico.

Estes factos revelam a capacidade limitada de previsibilidade que existe neste campo da atividade clínica, ao qual a cirurgia oncológica não é exceção. Com o intuito de contribuir para o esclarecimento da utilidade atual dos instrumentos de risco em doentes submetidos a cirurgia oncológica digestiva, no nosso primeiro trabalho, analisámos e comparámos o risco cirúrgico previsto pelo P-POSSUM Score, ACS NSQIP Surgical Risk Calculator, ASA e ARISCAT Risk Score [13]. Os nossos resultados revelaram que a precisão e a concordância dessas ferramentas eram limitadas. Num estudo idêntico envolvendo doentes com neoplasias malignas da cabeça e pescoço [14], também realizado pelo nosso grupo, verificámos que o instrumento ACS-NSQIP falhou na previsão de complicações, porém teve uma capacidade de discriminação aceitável para prever a mortalidade e o instrumento ARISCAT previu as complicações respiratórias de forma aceitável. Já os instrumentos ASA e P-POSSUM revelaram-se preditores fracos para mortalidade e morbidade.

Tudo isto coloca enormes desafios não só na altura de selecionar o instrumento adequado, mas também na confiança sobre a acurácia da informação gerada que se pretende que auxilie a decisão clínica. Uma forma de ultrapassar esta limitação (falta de acurácia) poderá passar por identificar as variáveis mais informativas de risco cirúrgico de cada um dos diferentes scores preditivos (e/ou incorporar outras), com o objetivo de otimizar a sua eficácia. Assim, no nosso primeiro trabalho, exploramos as variáveis que compõem cada instrumento e, com base nas mais informativas (idade, género, P-POSSUM fisiológico e complicação séria do ACS NSQIP), desenvolvemos um novo modelo de predição de risco cirúrgico, que denominámos MyIPOrisk-score. No training data set, o novo modelo demonstrou ter maior capacidade de discriminação dos doentes em risco de complicação major (AUC = 0,808; IC95%: 0,755-0,862) do que cada um dos instrumentos individualmente e apresentou a melhor associação entre o número de complicações major observadas versus previstas [13]. Já para a coorte de doentes com neoplasias malignas da cabeça e pescoço, o nosso novo modelo de previsão incluiu o ACS-NSQIP e ARISCAT (AUC=

0,750, IC95%: 0,63-0,87). Portanto, concluímos que há um valor limitado dos instrumentos de risco habituais quando analisados individualmente e que a combinação das variáveis mais informativas poderá ser útil para melhor predizer o risco de complicações graves, sendo que as variáveis discriminativas de risco, compreensivelmente, poderão variar com o tipo de cancro.

Como perspetivas futuras, consideramos ser de importância crucial e imediata a validação do MyIPOrisk-score em cirurgia oncológica digestiva (Figura 5).

Figura 5. Pathway de direcionamento de estudos futuros sobre CPO.

A direção futura dos estudos a realizar neste âmbito deve contribuir para esclarecer as problemáticas levantadas no nosso trabalho, direcionadas ao período pré- (validação prospetiva do MyIPOrisk-score e prehabilitação) e pós-operatório (utilidade profilática e terapêutica da VNI), de forma a propiciar uma prestação de cuidados verdadeiramente de qualidade, num processo contínuo para a obtenção dos resultados desejados em saúde.

Atendendo a que os dados que estão na base do nosso modelo foram recolhidos retrospetivamente, estamos de momento a realizar a sua avaliação prospetiva. Este passo é fundamental para que este recurso possa então ser transformado num instrumento de apoio a decisão clínica em oncologia na nossa população. Também, como destacado anteriormente, acreditamos que a baixa validade externa dos instrumentos atualmente em uso não é de estranhar, uma vez que a maioria foi desenvolvida há várias décadas, com métodos estatísticos pouco sofisticados, com base em variáveis/informações limitadas (em quantidade e qualidade) e não acompanha nem incorpora o dinamismo que caracterizada as características dos doentes, das técnicas cirúrgicas e anestésicas, dos meios

hospitalares disponíveis e regimes terapêuticos dos dias de hoje. As novas tecnologias associadas à inteligência artificial, a qual assenta na ideia de que os sistemas podem aprender com os dados, identificar padrões e tomar decisões, oferecem hoje novas oportunidades que virão certamente melhorar a estratificação de risco e aumentar a precisão preditiva dos instrumentos de risco, com o mínimo de intervenção humana [15, 16]. Nesse sentido, destacamos a colaboração estabelecida com o Instituto Superior Técnico da Universidade de Lisboa, com quem temos vindo a explorar as potencialidades destras tecnologias não só para validar, mas também para otimizar a efetividade e robustez do MyIPOrisk-score na previsão de CPO, tendo em vista melhorar o prognóstico perioperatório e a redução da mortalidade perioperatória. O projeto está já em curso e a análise preliminar dos dados evidência a existência de uma associação entre determinados padrões (de variáveis) com efeitos adversos (ex: complicações graves, mortalidade e tempo de internamento).

4.2 Caracterização os fatores de risco perioperatórios associados a complicações pulmonares graves de doentes submetidos a cirurgia abdominal

As complicações pulmonares são frequentes em doentes de risco submetidos a cirurgia abdominal em geral e a cirurgia oncológica digestiva em particular [17, 18]. Este tipo de complicação pode evoluir em termos de gravidade implicando a necessidade de suporte ventilatório e tem elevada morbimortalidade. Atendendo à sua elevada incidência e impacto negativo no prognóstico do doente oncológico, o nosso segundo trabalho focou-se na compreensão do perfil de risco perioperatório dos doentes que desenvolveram complicações pulmonares pós-operatórias graves, tendo necessitado de cuidados intensivos após cirurgia abdominal urgente ou eletiva [19]. Com o intuito de melhorar a identificação precoce destes doentes, estudamos ainda a associação entre os fatores de risco perioperatórios e a mortalidade associada. Verificámos que os doentes operados de forma eletiva e que desenvolveram complicações pulmonares no pós-operatório eram na sua maioria portadores de cancro digestivo. A mortalidade aos trinta dias foi de 21,7%. O risco de desenvolvimento

de complicações pulmonares no pós-operatório nas primeiras 48 horas esteve associado à necessidade de utilização de bloqueadores neuromusculares, gasometrias arteriais alteradas no pré-operatório. A desnutrição (baixa albumina) prévia à cirurgia associou-se a mortalidade em 30 dias. A incisão cirúrgica abdominal mediana, cirurgias prolongadas e um alto índice de massa corporal foram associados a complicações pulmonares pós-operatórias que ocorreram 48 horas após a cirurgia. Doentes com ASA 4 e com história de DPOC ou asma tiveram menos necessidade de ventilação mecânica no tratamento das complicações respiratórias.

A insuficiência respiratória aguda (IRA), enquanto entidade clínica resultante da evolução de CPP, pode em cirurgia oncológica digestiva assumir particular importância e relevância, e o ARDS, a sua expressão sindromática mais grave, assume-se como um verdadeiro desafio para a medicina intensiva, com uma taxa de mortalidade que pode chegar aos 76% [20]. Paralelamente aos estudos desenvolvidos no âmbito do presente trabalho, desenvolvemos investigação no sentido de melhor conhecer a epidemiologia e a evolução das complicações pulmonares graves em geral e da insuficiência respiratória aguda hipoxémica e do ARDS, em particular [21-28]. Participamos também na elaboração do Tratado Lusófono de Terapia Intensiva [29]. Os nossos estudos [21-28] sublinharam a necessidade de um melhor e mais precoce diagnóstico da ARDS. Foi notório a ausência de reconhecimento desta situação clínica, motivando sub-tratamento e uma alta taxa de mortalidade. Verificámos também que grau de envolvimento pulmonar tem impacto na evolução negativa ou positiva destes doentes. No nosso estudo, as o desenvolvimento de complicações pulmonares graves nas primeiras 48 horas do pós-operatório (com ou sem ARDS) associou-se à utilização repetida de bloqueadores neuromusculares durante a cirurgia, gasometrias arteriais alteradas no pré-operatório, incisão cirúrgica abdominal mediana, cirurgias prolongadas e um índice de massa corporal elevados. Estes aspetos exercem um efeito negativo na mecânica pulmonar, alterando as trocas gasosas e favorecendo o aparecimento de atelectasia pulmonar [30]. O perfil das CPP leva-nos a refletir sobre os potenciais benefícios da utilização profilática e terapêutica do suporte ventilatório mecânico sob pressão positiva não invasivo no período pós-operatório imediato.

O suporte respiratório não invasivo no tratamento da insuficiência respiratória aguda no período perioperatório pode incluir várias técnicas, nomeadamente oxigenoterapia convencional, cânula nasal de alto fuxo (HFNC) e ventilação não invasiva com pressão positiva (NIPPV) em particular a pressão positiva contínua nas vias aéreas (CPAP) e o Bilevel Positive Airway Pressure (BiPAP) [31]. Há evidência que no pós-operatório, a utilização de CPAP pode melhorar as trocas gasosas, não comprometendo a integridade das anastomoses gastrointestinais superiores [32]. Vários estudos demonstraram até que o uso profilático de BiPAP nas primeiras 12-24 horas após cirurgia de bypass gástrico em pacientes obesos mórbidos melhora significativamente a função pulmonar [33-37]. O BiPAP pode ultrapassar os problemas causados pela disfunção dos músculos respiratórios após a cirurgia abdominal superior a qual reduz as pressões máximas inspiratória e expiratória devido a fatores como irritação e inflamação ou trauma próximo ao diafragma, o que pode originar insuficiência mecânica local, inibição reflexa e dor. Estas são responsáveis por hipoventilação alveolar e retenção de CO_2 [38]. Huerta et al.[39], avaliaram a segurança e a eficácia do uso da CPAP após gastroplastia, não tendo sido observados casos de deiscência de anastomose.

Parece-nos assim razoável advogar que a utilização de NIPPV no pós-operatório de cirurgia digestiva oncológica pode ser útil para melhorar a oxigenação, não se antevendo o aumento da incidência de fístulas ou a deiscência de anastomose, desde que sejam empregues níveis adequados de pressão de insuflação. Isto significa indicações corretas, equipamento adequado e treino da equipa. Pretendemos desenvolver num futuro breve condições para avaliar o benefício desta intervenção terapêutica na mitigação das complicações pós-operatórias pulmonares (Figura 5).

4.3 Mitigação do risco de complicações pós-operatórias através de um programa de pré-habilitação

No nosso segundo trabalho, verificámos que os doentes de oncologia cirúrgica digestiva que desenvolveram complicações graves no pós-operatório tinham

uma performance física diminuída e a sua fragilidade era refletida nas variáveis fisiológicas dos instrumentos de risco estudados [19]. Observamos também que os fatores de risco mais importantes para as complicações são modificáveis e que a sua otimização pré-cirúrgica resultou na redução da taxa de complicações graves e da mortalidade pós-operatória. Os nossos resultados corroboram o papel relevante que tem vindo a ser progressivamente reconhecido à pré-habilitação [40-42]. Em termos de estratégia, a aposta na pré-habilitação revela-se inteligente e crucial. Enquanto intervenção multimodal, a pré-habilitação tem como objetivo principal aumentar a reserva funcional pré-operatória, melhorando assim a tolerância ao stress cirúrgico, o que se reflete na recuperação funcional pós-operatória mais rápida e na redução da incidência de complicações.

A premência da pré-habilitação é particularmente sentida nos doentes com comorbilidades crónicas e/ou síndromes geriátricos, onde a sua aplicação no período pré-cirúrgico permite de uma maneira geral melhorar os níveis basais dos parâmetros de saúde necessários para a cirurgia, mitigando o risco de CPO, podendo por si só melhorar os resultados dos cuidados de saúde, reduzir custos e diminuir as readmissões hospitalares [43-46]. Assim sendo, pretendemos acrescentar a pré-habilitação ao tratamento usual dos doentes considerados de risco. Para tal, desenvolvemos a nossa proposta de intervenção que será iniciada com um estudo piloto de pré-habilitação em doentes com adenocarcinoma da junção esófago-gástrica e do estômago que serão submetidos a cirurgia e envolvidos num programa de quimioterapia perioperatória (Figura 5). Para além de validarmos a eficácia do programa, estabelecemos como objetivo secundário, a avaliação do impacto da pré-habilitação domiciliar na capacidade funcional, estado de fragilidade, tolerância e eficácia do FLOT, qualidade de vida, incapacidade, CPO, mortalidade, tempo de internamento hospitalar, necessidade de UCI, readmissão hospitalar e local de alta. Este estudo fornecerá informações para orientar a realização de um futuro ensaio clínico multicêntrico aleatorizado para testar a eficácia da pré-habilitação na redução da morbidade e mortalidade pós-operatória nesta população.

Ao analisarmos as CPP, verificamos ainda que 18,3% dos doentes estudados e que evoluíram no período pós-operatório com CPP eram imigrantes dos PALOPs

[19]. A maioria deles tinha um nível socioeconómico baixo, o que nos levou a admitir que a condição social provavelmente tem uma importância não desprezível na génese das CPP observadas. Com o intuito de compreender melhor este subgrupo de doentes, fomos rever algumas publicações sobre os efeitos adversos à cirurgia referentes aos seus países de origem e região subsaariana, tendo-nos deparado com o artigo de Biccard et al. [47]. Nele, os autores descrevem uma taxa de mortalidade por CPO após cirurgia eletiva geral duas vezes superior à média global, apesar dos doentes serem mais jovens, terem um menor perfil de risco menor e uma taxa de complicações mais baixa. Para além dos aspetos organizacionais, de défice de recursos e treino, verificámos que uma parte importante dos doentes com uma evolução fatal tinham comorbilidades passiveis de serem minimizadas por um programa de pré-habilitação, o que motivou a realização de um ensaio, em que defendemos a necessidade de um programa de preabilitação adaptada àquela região [48].

4.4 Fatores limitantes da investigação e recomendações

Os estudos que constituem o corpo principal da tese incluíram uma amostra importante de doentes [14, 19, 29, 48]. As diversas variáveis estudadas foram objecto de avaliação com recurso ao processo clínico electrónico e avaliado por 3 investigadores independentes no sentido de diminuir a subjectividade. Apesar da revisão ter sido realizada retrospectivamente, o que pode permitir enviesamento de dados, foi construído um modelo de recolha de dados que foi seguido estritamente pelos investigadores. Foi determinada a metodologia e as definições a utilizar. Sempre que se constatou ausência de concordância o processo de revisão foi realizado pelos 3 investigadores em conjunto. As variáveis qualitativas a incluir nos distintos instrumentos de avaliação do risco, provieram de dados numéricos recolhidos de forma semelhante. Porém, este esforço metodológico não suplanta a realização de um estudo prospectivo em que a sistematização na recolha de dados é mais conseguida e programada.
Outro aspecto a ter em conta é que apesar de incluir um número importante de doentes o nosso estudo envolveu apenas uma instituição. Assim, a validação

das nossas conclusões deverá passar pela realização de um estudo semelhante mas de forma prospectiva e multicêntrica.

O facto do instrumento MyIPOrisck-score incluir no seu modelo uma variável obtida pelo instrumento ACS-NESQIP risk score, no qual não se conhece o algoritmo utilizado nos cálculos e o facto deste instrumento sofrer actualizações regulares poderia diminuir a sua validade. No sentido de avaliar se este aspecto conferia limitações ao nosso modelo, estudámos a nossa série com as versões distintas do instrumento e obtivemos os mesmos resultados. Este facto permite concluir que as actualizações não alteraram a variável que foi incluída no nosso modelo, essa variável é denominada taxa de Complicações Graves.

Uma das recomendações aos utilizadores do nosso modelo é que não devem introduzir dados na variável Surgeon Adjustment of Risks. Todos os casos por nós estudados foram calculados sem este ajustamento. Pretende-se assim não introduzir heterogeneidade na avaliação.

O tipo de cirurgia a introduzir no instrumento ACS foi sempre decidido pelos 3 investigadores em conjunto escolhendo o procedimento mais próximo aos realizados inclusive nos detalhes ou sempre que possível a cirurgia sobreponível. No sentido de validarmos a acuidade do nosso modelo aplicámo-lo em duas amostras diferentes de doentes que foram admitidos na unidade hospitalar em anos distintos. A área sob a curva obtida e a eficiência na previsão de complicações, foi semelhante nos dois grupos.

Apesar de estudarmos fundamentalmente a morbilidade utilizámos os dados da avaliação fisiológica obtidos pelo instrumento P-POSSUM que, como referimos na introdução, tem melhor acuidade para a previsão da mortalidade. A razão para esta decisão aparentemente contradiória, prende-se com o facto de que nos nossos estudos o instrumento POSSUM subestimava a taxa de complicações ao contrário do que era obtido quando utilizávamos o instrumento P-POSSUM.

O nosso modelo associou um risco mais elevado de complicações a doentes menos idosos. Este facto é aparentemente um contra-senso mas explica-se porque na população menos idosa (<70 anos) a radicabilidade cirúrgica, isto é procedimentos cirúrgicos mais agressivos e extensos são mais vezes realizados.

Este tipo de procedimentos associam-se, como é usual, a uma maior probabilidade de complicações.

O instrumento por nós desenvolvido (MyIPOrisk-score) revelou maior acuidade ao comparámos a taxa de complicações prevista com a real, do que a observada com o P-POSSUM, ACS-NESQIP e ARISCAT. Porém, é imperioso como já referimos validarmos os nosso resultados num estudo perspectivo e multicêntrico.

4.4.1. Perspetiva futura

A nossa série de doentes ("dataset") está no presente momento a ser estudada com recurso a metodologias de inteligência artificial. Os modelos de aprendizagem automática revelaram-se bastante interessantes e atrativos na deteção de padrões em dados complexos e heterogéneos de elevada [49]. Com o objetivo de estender e melhorar as previsões do risco pós-cirúrgico em doentes com cancro obtidas através da ferramenta "MyIPOriskScore", foram explorados alguns modelos baseados em aprendizagem automática ("machine learning"). Numa primeira abordagem, estamos a analisar a quantidade de "features" existentes no nosso "dataset" e foi feita uma limpeza/pré-processamento aos dados, tendo em conta algumas inconsistências e erros de "input" encontrados (e.g. 14,.8 ou 2,2,). Para lidar com os "missing values" no "data" e imputar estes, foi utilizada uma técnica multi-variável disponível através da biblioteca "scikit learn" para a linguagem de programação Pyhton. Posteriormente, foram implementados alguns algoritmos mais populares em aprendizagem automática (classificadores) de uma forma exploratória com o objetivo de prever se um doente irá ter (ou não) alguma probabilidade de CPO (classe objetivo "complicação pós-cirúrgica") tendo em conta o conjunto de fatores da nossa base de dados clínicos. Entre os classificadores disponíveis no sklearn (biblioteca em python) foram utilizados: Naive Bayes, K-Nearest Kneighbours, Support Vector Machines, Decision Trees, Random Forests e o Multi-Layer Perceptron [50-53]. Como forma de avaliar a performance destes modelos foram utilizadas as seguintes métricas:

- RMSE (Root Mean Square Error), MAE (Mean Absolute Error) e MAPE (Mean Absolute Percentage Error).

Os dados obtidos em breve serão objecto de publicação. Em termos de trabalho futuro no que diz respeito aos modelos de classificação serão ajustados os parâmetros dos vários modelos (e.g. pesquisa Bayesiana) [51, 54] e explorados quais as “features” são relevantes para o processo de classificação, e quais poderão ser descartadas para reduzir a dimensionalidade do conjunto de dados. O objetivo é construir um instrumento cada vez mais robusto na definição do risco cirúrgico dos doentes com patologia oncológica digestiva que podem beneficiar de tratamento cirúrgico curativo.

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Capítulo V - ANEXOS

5.1 Anexo I: Trabalho original V

Optimizing classical risk scores to predict complications in head and neck surgery: a new approach

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Objetivo: Validar ferramentas para identificar doentes em risco de complicações perioperatórias para implementar programas de pré-reabilitação em cirurgia de cabeça e pescoço (C&P).
Métodos: Coorte retrospetiva incluindo 128 doentes submetidos a crurgia de C&P, com internamento em Unidade de Cuidados Intermédios pós-operatórios. A precisão dos scores de risco ASA, P-POSSUM, ACS-NSQIP e ARISCAT para prever complicações pós-operatórias e mortalidade foi avaliada. Uma análise multivariável foi subsequentemente realizada para criar uma nova ferramenta de previsão de risco modelo para CPO no IPO-Porto.
Resultados: A nossa morbilidade e mortalidade em 30 dias foi de 45,3% e 0,8%, respetivamente. O ACS-NSQIP falhou em prever complicações e está associado a uma capacidade de discriminação aceitável para prever a morte. A habilidade de discriminação de ARISCAT para prever complicações respiratórias foi aceitável. Os scores ASA e P-POSSUM revelaram-se fracos preditores de mortalidade e de morbilidade. O nosso novo modelo de previsão incluiu o ACS-

NSQIP e ARISCAT (área sob a curva 0,750, intervalos de confiança de 95%: 0,63-0,87).

Conclusão: Apesar do valor insuficiente dessas calculadoras de risco quando analisadas individualmente, projetamos uma ferramenta de risco combinando-as que melhor prevê o risco de complicações graves.

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HEAD AND NECK

Optimizing classical risk scores to predict complications in head and neck surgery: a new approach

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Abstract

Purpose To validate tools to identify patients at risk for perioperative complications to implement prehabilitation programmes in head and neck surgery (H&N).

Methods Retrospective cohort including 128 patients submitted to H&N, with postoperative Intermediate Care Unit admittance. The accuracy of the risk calculators ASA, P-POSSUM, ACS-NSQIP and ARISCAT to predict postoperative complications and mortality was assessed. A multivariable analysis was subsequently performed to create a new risk prediction model for serious postoperative complications in our institution.

Results Our 30-day morbidity and mortality were 45.3% and 0.8%, respectively. The ACS-NSQIP failed to predict complications and had an acceptable discrimination ability for predicting death. The discrimination ability of ARISCAT for predicting respiratory complications was acceptable. ASA and P-POSSUM were poor predictors for mortality and morbidity. Our new prediction model included ACS-NSQIP and ARISCAT (area under the curve 0.750, 95% confidence intervals: 0.63–0.87).

Conclusion Despite the insufficient value of these risk calculators when analysed individually, we designed a risk tool combining them which better predicts the risk of serious complications.

Keywords P-POSSUM · ACS-NSQIP · ASA · ARISCAT · Head and neck

Introduction

Major surgery implies significant homeostatic disturbance to the patient and it is well established that patients who experience postoperative complications within 30 days of surgery have a reduced long term survival rate [1, 2]. Furthermore, even in the absence of complications there is a

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20–40% reduction in postoperative physical function and a significant deterioration in the quality of life after major surgery [1, 3].

It has long been accepted that individuals who have limited pre-operative physical fitness have higher rates of morbidity and mortality during their hospital stay [4, 5]. On the other hand, individuals who have better preoperative physical fitness experience less postoperative pain and have better physical functional status postoperatively [6]. For this reason, there has been a growing interest in the concept of prehabilitation which is defined as a multidimensional programme that aims to optimize physical functionality preoperatively to achieve a quicker recovery of functional status in the postoperative period [7]. Prehabilitation has a patient-centered strategy, focused on optimizing patient eligibility for surgery and improving surgical outcomes [7]. Some authors state that prehabilitation is analogous to marathon training [1]. In fact, they both require training. Similar to marathon training, prehabilitation programmes acknowledge the multidimensional aspects of preoperative preparation to include nutritional, psychological, and behavioural interventions in addition to exercise [1].

Various scoring systems have been developed to estimate the risk of perioperative morbidity and mortality and these might be valuable in the selection of patients for prehabilitation before surgery. This is particularly important in the head and neck oncology discipline where complications such as fistula development can result in the significantly extended length of stay and decreased quality of life [8].

The American Society of Anesthesiologists physical status (ASA) is perhaps the best known and widely used grading system for preoperative health of the surgical patients [9]. It relies on a subjective assessment of a patient's overall health that is based on six classes, with ASA I being a normal healthy patient, and ASA VI a brain-dead patient [9] (Appendix A).

Another scoring system is the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM) which was initially developed by Copeland et al. and later adjusted in 1998, into Portsmouth-POSSUM (P-POSSUM) [10, 11]. It aimed to provide both retrospective and prospective analysis of the risk of mortality and morbidity of surgical patients within 30 days after surgery and to facilitate surgical audit and comparison of the performance of individual units. The P-POSSUM score includes 18 parameters divided into two components; 12 physiological and 6 operative factors, to make a minimum score of 18 and a maximum score of 136 and then converted to a percentage with a logistic regression [10, 11] (Appendix B).

More recently, the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) developed an universal surgical risk calculator based on preoperative risk and postoperative morbidity and mortality [12, 13]. This risk calculator is an open-access online tool that accepts the input of 21 comorbidity and demographic-related, patient-specific variables, in conjunction with a surgery-specific Current Procedure Terminology code, to predict patients' risk of 12 postoperative outcomes within 30 days after surgery (Appendix C).

Likewise, the acknowledgment that postoperative pulmonary complications can contribute significantly to overall perioperative morbidity and mortality, motivated the development of The Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk scale [14]. The ARISCAT score predicts the overall incidence of postoperative pulmonary complications, by assigning a weighted point score to four patient-related factors and three surgical procedure-related factors [14] (Appendix D). It finally categorizes risk as follows: Low risk (0–25points), Intermediate risk (26–44 points) and High risk (45–123 points).

Over the years, the aforementioned risk tools have been studied in head and neck surgery with conflicting results. Therefore, we have evaluated these surgical risk calculators comparing several predicted outcomes with the observed outcomes in our population, to develop a model to estimate the degree of risk and afterwards implement prehabilitation programmes in our institution.

Material and methods

The medical records of all patients submitted to head and neck major surgery with Intermediate Care Units (IMCU) admittance for postoperative care, in a tertiary care hospital, from January 2016 to December 2017, were retrospectively reviewed. An additional cohort of patients admitted in 2018, was included for validation purposes of our risk model.

The admittance to the IMCU was due to the complexity of the surgical procedure and/or due to comorbidities of patients.

The following surgical risk calculators were used: P-POSSUM, ACS-NSQIP, ASA and ARISCAT, to predict the risk of postoperative outcomes [9–12, 14]. In this study, on-line calculator tools were used to obtain P-POSSUM scores (www.riskprediction.org.uk) and ACS-NSQIP scores (www.riskcalculator.facs.org) [13, 15]. Clinical information was manually entered into the study database. For the ACS-NSQIP risk calculator, the most relevant Current Procedural Terminology (CPT) codes were selected based on the type, extent, and attributes of the procedure. When multiple procedures were performed that could not be captured by a single code, the principal CPT code, after consultation with the surgeon, that represented the most clinically complex procedure among all procedures done during that operation,

was chosen. To maintain consistency, "Surgeon Adjustment of Risk" was not altered.

The occurrence of postoperative complications within 30 days was registered. The severity of complications was evaluated using Clavien-Dindo (none/minor if inferior or equal to grade 2 and major if equal or superior to grade 3) and ACS-NSQIP ("any complications'' or "serious complications'') classifications [12, 16, 17]. The ACS-NSQIP defines "serious complications'' as the presence of any of the following: cardiac arrest, myocardial infarction, pneumonia, renal insufficiency and failure, pulmonary embolism, deep venous thrombosis, return to the operating room (OR), deep incisional surgical site infections, organ space surgical site infections, systemic sepsis, unplanned intubation, urinary tract infection, and wound disruption. "Any complication'' was defined as superficial incisional surgical site infections, stroke, or ventilator support > 48 h or any of the aforementioned serious complications [12]. In cases with multiple complications, the case was assigned a grade corresponding to the highest graded complication according to Clavien-Dindo and ACS-NSQIP classifications.

The hospital length of stay (LOS) and mortality (at 1 and 12-months after surgery) were also evaluated. Despite the fact that the risk instruments included in this study were designed to predict 1-month mortality, only one patient died in the first month after surgery in our sample. Therefore, the analysis of the 1-month mortality was not feasible. Although not the most recommended, we decided to analyse the 1-year mortality using the same risk tools.

The body mass index, a variable included in the ACS-NSQIP score, was also included and analysed individually in this study.

The study was approved by the Institutional Review Board and the Ethics Committee of the hospital. The protocols conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki (version 2002).

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies and percentages.

Chi-squared or Fisher's exact tests were used to evaluate the association between two categorical variables, namely, the occurrence of postoperative complications (within 30 days after surgery) or death (within 30 days and 1 year after surgery) with different categories of ASA score and ARISCAT.

Comparisons between groups were performed, using independent samples t-tests (or Mann–Whitney) and ANOVA (or Kruskal Wallis) tests for continuous variables as appropriate. P-POSSUM and ACS-NSQIP scores were compared between patients with the occurrence of postoperative complications within 30 days. Body mass index, P-POSSUM and ACS-NSQIP scores were compared between patients with the occurrence of death within 1-year after surgery.

Survival analysis after surgery of patients with different ASA categories was performed using the Kaplan–Meier methodology.

The ability of the risk tools P-POSSUM, ACS-NSQIP and ARISCAT for predicting post-operative complications and death was assessed using Receiver Operating Characteristic (ROC) curves and estimating the area under the curve (AUC). The discrimination ability of each score was considered acceptable for $0.7 \leq AUC < 0.9$ and excellent for $AUC \geq 0.9$ [18]. The 95% confidence intervals (CI) are reported.

Binary logistic regression analysis was performed to evaluate the association of each risk score with the occurrence of major complications (Clavien-Dindo classification ≥ 3 and Serious complication according to ACS-NSQIP score). An univariable model was first built for each score. Then a multivariable model was built using a stepwise variable selection algorithm which retained in the final model only the significant variables. The prediction ability of the final panel of variables was also evaluated using ROC curves and the corresponding AUC.

Significance was settled for $p < 0.05$.

Statistical analysis was performed using the SPSS software, version 22.

Results

Demographic and clinical characterization

There were 128 patients submitted to surgery in the first period of study. Of these, 106 (82.8%) were male and 22 (17.2%) were female. The mean (standard deviation) age of patients was 62.6 ± 10.1 years (min–max 41–91 years).

The mean LOS, in days, was 2.1 ± 2.2 (min–max 1–18 days) in the IMCU and globally in the Institution was 22.0 ± 19.1 (min–max 2–113 days).

Most patients were admitted for elective surgery (93%, $n = 119$). Six patients needed unplanned Intensive Care Unit Admission (4.7%, $n = 6$).

Most patients were independent (84.4%, $n = 108$) or partially dependent (9.4%, $n = 12$) with only eight patients being totally dependent (6.3%) for the activities of daily living.

Around 23% of our patients presented *Diabetes Mellitus* ($n = 29$). The majority of these ($n = 26$) was under oral medication and only three patients were performing insulin treatment. Almost 60% ($n = 76$) presented hypertension requiring medication and 21% ($n = 27$) had a history of congestive heart failure 30 days prior to surgery. Over 40% ($n = 53$)

were active smokers in the previous year and 28.1% ($n=36$) had severe chronic obstructive pulmonary disease history. Around 30% ($n=40$) presented dyspnea within 30 days of surgery. None had a history of dialysis or systemic sepsis within 48 h prior to the procedure.

The most common procedures which required admittance in the IMCU in our series were laryngectomy (16.4%), glossectomy with surgical excision of the floor of mouth (13.3%), COMMANDO operation (7.8%) and pharyngolaryngectomy (6.3%). The surgical procedures of our sample are summarized in Table 1.

Fifty-eight patients experienced one or more postoperative complication within 30 days after surgery (45.3%) (Fig. 1). The most common postoperative complication was surgical infection (31.0%; $n=18$), followed by respiratory infection or insufficiency (25.9%, $n=14$). Respiratory insufficiency was defined as postoperative $PaO_2 < 60$ mmHg and/or $PaCO_2 > 50$ mmHg. When we analyse the complications, according to Clavien-Dindo classification, most patients presented grade II (i.e., requires pharmacological treatment, 28.1%), grade IIIb (i.e., requires surgical treatment under general anesthesia, 6.3%) and IVa (i.e., life Threatening complication-single organ dysfunction, 3.9%). Globally, the incidence of major postoperative complications according to Clavien-Dindo Classification (grade equal or superior to grade III) was 14.8% ($n=19$). Twenty-two patients (17.2%) presented a serious complication according to the ACS-NSQIP classification.

Thirty-nine patients died during the study period: one died in the first month after surgery (overall mortality at 1-month of 0.8%) and 29 patients died in the first year (22.7%).

We analysed the effect of the nutritional status in the 1-year mortality. Patients with death in the first year after surgery had a significantly lower mean body mass index (22.9±3.9 Kg/m^2) than patients who survived (25.3±4.9 Kg/m^2) (p=0.006).

Five patients (3.9%) had prior chemoradiation, six patients (4.7%) had a history of radiotherapy only and seven patients (5.5%) had a history of chemotherapy only. There was no association between history of prior chemo and/or radiotherapy and the occurrence of postoperative complications ($p>0.05$). On the other hand, prior radiotherapy was associated with 1-year mortality ($\chi^2=6.22$; $p=0.010$).

The cohort of patients subsequently added to the original sample for validation purposes consisted of 45 patients and was similar to the training cohort considering major demographic and clinical characteristics.

ASA physical status

Most of the patients were ASA 2 (50.8%) and 3 (47.7%), with only two patients being ASA 4 (1.6%). Of the 58 patients who presented postoperative complications, 25 were ASA 2, 31 were ASA 3 and 2 were ASA 4. Of the 18 patients presenting major complications according to the Clavien-Dindo classification (grade ≥ 3), the majority were ASA 3 ($n=13/61\%$). No significant association between ASA score and the occurrence of complications was found ($p=0.111$).

A higher ASA score was positively associated with 1-year mortality ($p=0.005$). In fact, in the first year after surgery, 16.2% of the ASA two patients, 34.4% of the ASA three patients and 100% of the ASA four patients, died.

P-POSSUM

The overall P-POSSUM predicted morbidity rate was 47.93 (±23.93)% and the predicted mortality rate was 6.42 (±11.36)%. This means that the P-POSSUM scoring system predicted that 61 patients would develop postoperative complications (47.9%), comparing with the 58 (45.3%) patients who did effectively had complications and that eight patients were expected to die (6.42%), but only one patient did effectively died in the first month after surgery (0.8%).

The physiological and operative severity scores were compared between patients with and without death 1-year after surgery, and no significant differences between groups were observed ($p=0.100$ and $p=0.253$, respectively) (Table 2). Also, there were no differences between these groups considering the predicted mortality rate ($p=0.116$).

The predicted morbidity rate was significantly higher in patients who died in the first year after surgery ($p=0.049$) (Table 2). P-POSSUM mortality discrimination ability was only reasonable according to the analysis of ROC curves (AUC 0.60; 95% CI 0.49–0.71).

The physiological and operative severity scores were compared among patients with and without complications after surgery, and no differences between groups were observed ($p=0.499$ and $p=0.698$, respectively) (Table 2). In addition, there were no differences between these groups considering the predicted morbidity rate ($p=0.675$). P-POSSUM discrimination ability for serious complications according to ACS-NSQIP classification and major complications according to Clavien-Dindo classification was only reasonable (AUC 0.63; 95% CI 0.48–0.77 and AUC 0.69; 95% CI 0.58–0.81, respectively).

ACS-NSQIP

Patients who developed complications in the postoperative period presented a higher predicted ACS-NSQIP risk of complications pre-operatively, specifically the risk of severe complication ($p=0.001$), any complication ($p<0.001$), risk of surgical site infection ($p=0.030$), risk of pneumonia ($p=0.170$) and risk of cardiac complications ($p=0.040$) (Table 3).

Table 1 Head and Neck procedures with Intermediate Care Unit admittance

Most common procedures with ICU admittance	*n*	Relative Frequency (%)	Associated procedures	
Laryngectomy	21	16.4	Neck dissection	16
	Partial 7		Reconstruction (pedicled flap)	1
	Total 14		Thyroidectomy	2
Pharyngolaryngectomy	8	6.3	Neck dissection	7
			Reconstruction (pedicled flap)	2
			Thyroidectomy	1
Glossectomy with surgical excision of floor of mouth	17	13.3	Mandibulectomy	10
			Neck dissection	15
			Reconstruction (pedicled flap)	7
			Reconstruction (free flap)	2
			Tracheostomy	10
Glossectomy	15	11.7	Reconstruction (pedicled flap)	4
			Reconstruction (free flap)	1
			Tracheostomy	1
			Neck dissection	6
			Pharyngectomy	1
COMMANDO operation	10	7.8	Reconstruction (pedicled flap)	7
			Tracheostomy	2
Mandibulectomy	12	9.4	Reconstruction	9
			Tracheostomy	3
			Neck dissection	2
			Surgical excision of floor of mouth	1
Partial pharyngectomy	11	8.6	Neck dissection	10
			Tracheostomy and glossectomy	1
Maxilectomy	7	5.5	Neck dissection	1
			Reconstruction (pedicled flap)	1
			Orbital exenteration	1
			Orbital enucleation	1
			Pharyngectomy and glossectomy	1
Total parotidectomy	1	0.8	Reconstruction (pedicled flap)	1
Endoscopic resection of malignant sinonasal tumours	2	1.6		
Excision of malignancy from the lip with reconstruction	5	3.9	Neck dissection	1
Revision of hemostasis from the surgical wound	3	2.3		
Suspension microlaryngoscopy with biopsy	6	4.7	Neck dissection	1
Total tiroidectomy	1	0.8	Neck dissection	1
Partial rhinectomy	1	0.8	Neck dissection and Reconstruction with local flap	
Neck dissection	4	3.1	Reconstruction (pedicled flap)	1
Tracheostomy	1	0.8		
Deep neck abscess drainage	1	0.8		
Trans-oral epiglotectomy	1	0.8		
Removal of osteosynthesis material from the mandible	1	0.8		

ACS-NSQIP did not show discrimination ability for predicting surgical site infection (AUC 0.47; 95% CI 0.29–0.65) and pneumonia (AUC 0.59; 95% CI 0.40–0.78) and had a reasonable accuracy for cardiac complications in our sample (AUC 0.65; 95% CI 0.48–0.82).

The mean predicted ACS-NSQIP risk of death was significantly higher in patients who died (4.58 ± 8.12 versus 1.13 ± 1.93, $p = 0.020$). The ACS-NSQIP discrimination ability for predicting the risk of death in the postoperative period was acceptable (AUC 0.74; 95% CI 0.65–0.84).

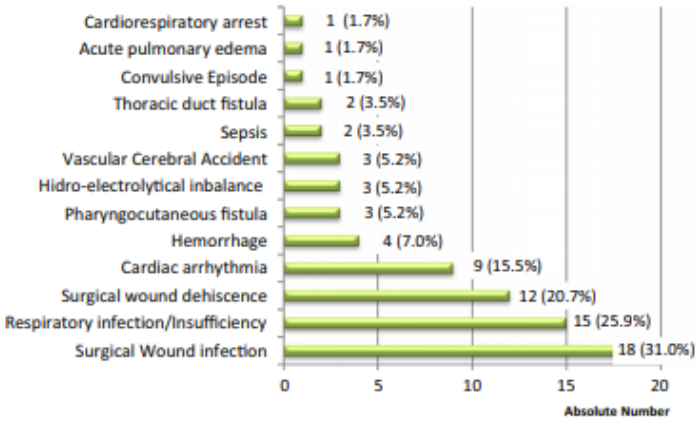

Fig. 1 Postoperative complications in patients submitted to Head and Neck surgery with Intermediate Care Unit admittance ($n = 58$ patients)

Table 2 Comparison of P-POSSUM scores among patients considering mortality and morbidity parameters

P-POSSUM predicted risk		Physiological Score P-P	Operative severity score	% mortality P-POSSUM	% morbidity P-POSSUM
Death 1 -year after surgery	No ($n = 94$)	20.5 ± 6.0	12.9 ± 3.1	5.2 ± 8.7	45.4 ± 23.1
	Yes ($n = 34$)	23.2 ± 8.3	13.6 ± 3.5	9.9 ± 16.4	54.8 ± 25.2
	p value	0.100	0.253	0.116	0.049
30-day post-operative complications	No ($n = 70$)	20.9 ± 6.5	13.0 ± 2.9	5.4 ± 7.5	47.1 ± 23.7
	Yes ($n = 58$)	21.7 ± 7.1	13.2 ± 3.6	7.6 ± 14.7	48.9 ± 24.3
	p value	0.499	0.698	0.296	0.675

Table 3 Comparison of ACS-NSQIP predicted risks among patients with the occurrence of complications and death

ACS-NSQIP predicted risks	Postoperative Complication		p value	AUC (CI)
	No ($n = 70$)	Yes ($n = 58$)		
Severe Complication	17.3 ± 10.6	24.3 ± 11.6	< 0.001	0.69 (0.58–0.81)
Any Complication	19.0 ± 12.3	27.6 ± 12.3	< 0.001	0.59 (0.48–0.70)
Surgical Site Infection	5.8 ± 5.9	8.2 ± 6.2	0.025	0.47 (0.29–0.65)
Pneumonia	3.7 ± 3.4	5.3 ± 4.0	0.170	0.59 (0.40–0.78)
Cardiac complications	0.7 ± 0.8	1.5 ± 1.9	0.040	0.65 (0.48–0.82)
	Death 1-year after surgery		p value	AUC (CI)
	No ($n = 94$)	Yes ($n = 34$)		
Risk of death	1.13 ± 1.93	4.58 ± 8.12	0.020	0.74 (0.65–0.84)

ARISCAT

The mean ARISCAT score in our sample was 16.2 ± 10.3, ranging from 0 to 39. Therefore, there were no patients in the preoperative high-risk category (score ≥ 45).

Patients who developed pulmonary complications had significantly higher (24.1 ± 9.7) preoperative ARISCAT score than patients without (15.1 ± 9.9) this complication ($p = 0.001$).

In 41 patients with intermediate preoperative ARISCAT score, 12 (29.3%) developed pulmonary complications (Table 4). Patients with low-risk scores had lower rates of pulmonary complications (4.6%) than those in the intermediate-risk group (29.3%), with statistically significant differences ($p = 0.001$) (Table 4).

Table 4 Comparison of ARISCAT predicted risk scores among patients with the occurrence of respiratory complications and death after surgery

Outcome		ARISCAT predicted risk		*p* value
		Low risk (< 26 points)	Intermediate risk (26–44 points)	
Respiratory Complication	Yes ($n = 16$)	4	12	0.001
	No ($n = 112$)	83	29	
Death 1-year after surgery	Yes ($n = 34$)	22	12	0.905
	No ($n = 94$)	65	29	

Table 5 Estimated Odds Ratio of Serious Complications (ACS classification) using uni- and multivariable binary logistic regression models

Variable		Univariable OR (95% CI)	Multivariable OR (95% CI)
ARISCAT		1.07 (1.02–1.12)	1.06 (1.01–1.11)
ACS		1.05 (1.02–1.09)	1.05 (1.01–1.09)
P-POSSUM		1.00 (0.88–1.13)	–
ASA	2	1	
	3	2.01 (0.87–4.62)	–

The discrimination ability of ARISCAT score for predicting respiratory complications was acceptable (AUC 0.75; 95% CI 0.61–0.88).

ARISCAT score was not associated with death 1-year after surgery ($p = 0.905$), nor were there differences of the ARISCAT score between the individuals with and without death after surgery ($p = 0.905$). (Table 4).

Multivariable analysis

A binary logistic regression model was built to predict the occurrence of major complications within 30 days after surgery (according to ACS-NSQIP classification), considering as potential independent variables the risk tools: P-POSSUM, ACS-NSQIP, ASA and ARISCAT.

Only ACS-NSQIP and ARISCAT were found statistically significant in the multivariable model and have been included in the final model (Table 5). The occurrence of serious complications increases significantly with ACS-NSQIP score and ARISCAT score (OR = 1.05; 95% CI 1.01–1.10 and OR = 1.08; 95% CI 1.02–1.15, respectively). The AUC obtained with this model for the training set (patients admitted in the period 2016–2017) was 0.75 (95% CI 0.63–0.87) (Fig. 2a). A cut-off between low and high risk was chosen to maximize sensitivity with an acceptable specificity. For the chosen cut-off a sensitivity of 81.8% and a specificity of 54.8% were obtained for the training set.

Given the small sample size of the original training set, we decided to append an additional dataset of 45 patients admitted in 2018, that was subsequently included for validation purposes to have a larger sample and to refit the model. A sensitivity of 82.8% and a specificity of 52.8% were obtained. The results are presented in Fig. 2b and Table 5.

No significant model was obtained considering the classification of Clavien-Dindo and the risk tools P-POSSUM, ACS-NSQIP, ASA and ARISCAT.

Discussion

Accurate estimates of postoperative complication risks are undoubtedly important to patients, caregivers, and clinicians. To our knowledge, this is the first study performing a comprehensive analysis of the four most important risk scores in the surgical community, ASA, P-POSSUM, ACS-NSQIP and ARISCAT in head and neck procedures. We have studied the theoretically considered high-risk patients, by including patients admitted in the IMCU for postoperative care due to anesthetic or surgical risk. Given the questionable value of the risk scores individually evaluated in this study, we performed a multivariate analysis combining them and designed a new risk tool for our institution which better predicts the risk of serious complications in our patients.

The topic of surgical complications and mortality is a relatively delicate and difficult to report subject. However, our crude 30-day morbidity and mortality were broadly consistent with those in other published reports, at 45.3% and less than 1%, respectively [19–21]. Globally, the incidence of major postoperative complications according to the Clavien-Dindo classification (grade equal or superior to grade 3) was 14.8% ($n = 19$) which is also in line with other reports [19, 20].

The ASA classification was established in the 1940s and has since undergone multiple revisions [22]. Today, the ASA classification is universally recorded for any surgical case performed under anesthesia. While not intended to predict risk, increasing ASA class has been associated with increased perioperative morbidity and mortality [9, 22, 23]. It is also included in other surgical risk calculators, as ACS-NSQIP [12]. In our sample, the ASA score was not associated with the occurrence of complications ($p = 0.111$). However, the association between the ASA score and postoperative complications has been reported in the literature in many surgical specialties, including Otorhinolaryngology. Hackett and colleagues confirmed the potential of ASA score for risk stratification not only for medical complications but also for mortality after surgery. The same study

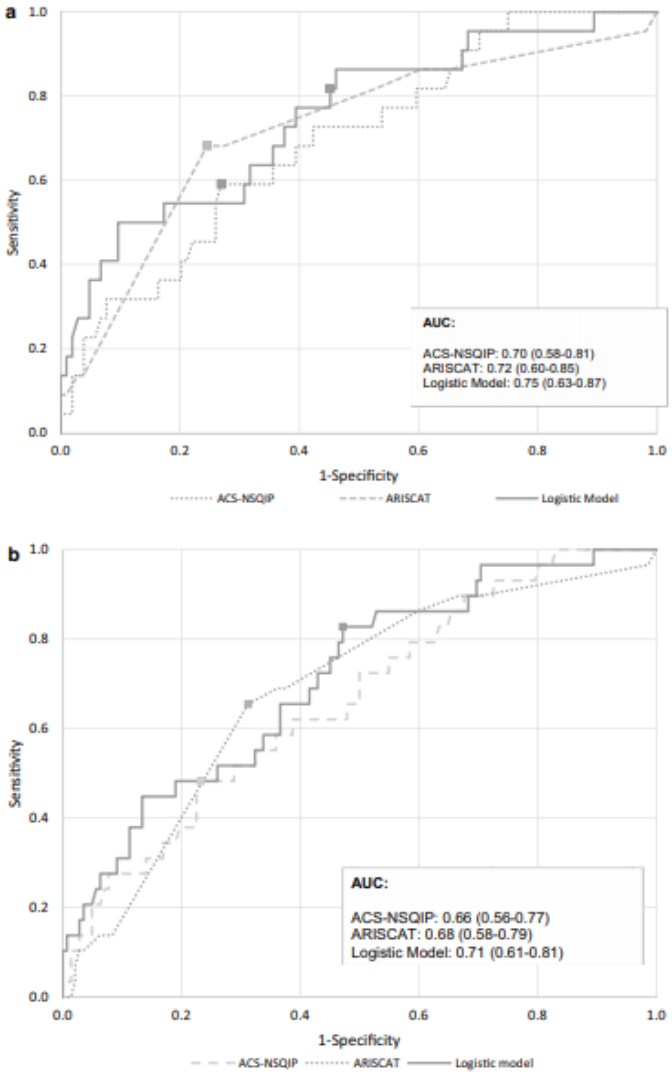

Fig. 2 **a** Receiver-operating characteristic curves and performance metrics for our algorithm in predicting the occurrence of serious complications in the training set of patients ($n = 128$). **b** Receiver-operating characteristic curves and performance metrics for our algorithm in predicting the occurrence of serious complications in a larger sample of patients (original training set plus an additional dataset of 45 patients, $n = 173$)

reported that patients with greater ASA classes developed substantially higher rates of postoperative medical complications and mortality when compared to patients in lower ASA classes [22]. In our study, a higher ASA score was positively associated with 1-year mortality ($p = 0.005$) and a lower survival time was observed in patients with higher ASA grades. In spite of the ASA classification being simple and widely understood, a great variability between assessments has been reported as it relies on a subjective evaluation [24]. Also, it does not describe individual patient risk and cannot, therefore, account for a surgical procedure, preoperative optimization or individual differences in postoperative care setting [24, 25]. Nevertheless, the ASA classification system is a simple, valid metric for determining the risk

of complications and mortality, being extremely useful for clinical communication between colleagues. However, we agree that for more detailed case analysis, for auditing, risk management and funding allocation purposes, ASA classification is insufficient [24].

The P-POSSUM system has been recommended as an accurate method in evaluating surgical outcomes and allowing direct comparisons, despite distinct patterns of referral and populations. It has the advantage of being simple and including variables that are easy to collect. It considers the physiological condition of the patient at admission and the severity of the surgical procedure to predict the rates of morbidity and mortality. It has been already evaluated in head and neck surgery with controversial results. In our study, P-POSSUM discrimination ability for mortality and morbidity was only reasonable according to the analysis of ROC curves. Also, there were no differences between groups with and without complications within 30 days after surgery or death until 1-year after surgery considering the physiological and operative severity scores and also considering the predicted morbidity and mortality rates, respectively. In our sample, P-POSSUM overpredicted 30-day mortality, as a total of eight deaths were predicted but only one occurred. Other authors reported that P-POSSUM overpredicted the occurrence of death and had no relevance in predicting mortality in a population undergoing head and neck surgery [20, 26]. However, the analysis of mortality in our study is limited by the small number of patients who died in a relatively reduced sample. Also, P-POSSUM slightly overpredicted morbidity, as a total of 61 patients were predicted to develop postoperative complications (47.9% morbidity rate) but only 58 effectively did (45.3%). Other colleagues reported divergent results in head and neck surgery for P-POSSUM. Ribeiro and Kowalski used the original POSSUM score to predict complications in 530 patients having orofacial surgery for cancer [21]. The findings in this study mirror those of Griffiths et al. who, in a similar population, reported that POSSUM under-predicted morbidity in the low to moderate risk categories [21, 26]. More recently, Tighe audited 360 operations in 245 patients submitted to orofacial surgery for cancer and concluded that P-POSSUM under-predicted morbidity in the low-risk groups and over-predicted mortality in all risk groups [20]. Unfortunately, in our study, P-POSSUM has revealed itself not suited to predict outcomes in head and neck surgery. Indeed, the variables that comprise the P-POSSUM scoring system were designed for a general surgical population, and variables like "peritoneal soiling" and the "Glasgow Coma Scale" are probably not relevant to head and neck surgery. Remarkably, poor nutritional status is another factor shown to be significantly associated with postoperative mortality in our sample. Considering the similar results of other studies in the head and neck cancer population, we consider that the inclusion of the variable "nutritional status" in the P-POSSUM score should be equated [26, 27]. Griffiths et al. also suggested that radiotherapy and previous surgery were both significant for the development of postoperative complications and were worthy of inclusion in the original Possum score for head and neck surgery [26]. In our sample, previous radiotherapy was not associated with the occurrence of postoperative complications, possibly due to our small sample size. On the other hand, prior radiotherapy was associated with 1-year mortality.

Considering the ACS-NSQIP calculator in our patients, one may conclude that it had an insufficient accuracy for predicting complications. In spite of the existence of significant differences for the ACS-NSQIP predicted risks between groups with and without specific complications, the discrimination ability for predicting the most common complications (surgical site infection, pneumonia and cardiac complications) is nearly reasonable or worse. Regarding mortality, although ACS-NSQIP was not designed to predict 1-year mortality, it showed an acceptable discrimination ability for predicting the risk of death in the postoperative period in our sample. Also, the predicted ACS-NSQIP risk of death was significantly higher in patients who died ($p = 0.020$). There have been studies previously showing that the ACS-NSQIP database may not adequately predict postoperative complications in complex surgical procedures. Prasad et al. concluded, in a cohort of 98 patients, that ACS-NSQIP risk calculator was a poor predictor of perioperative complications following major head and neck operations [28]. Other two recent studies pertaining to microvascular head and neck reconstruction showed poor prediction performance of ACS-NSQIP [29, 30]. In addition, Schneider et al. have added total laryngectomy to the list of complex procedures for which the NSQIP risk calculator may not be as accurate in predicting postoperative adverse events [31]. More recently, Vosler et al. evaluated 131 patients and reported efficacy of ACS-NSQIP surgical calculator for predicting postoperative complications in head and neck oncology surgeries that do not require microvascular reconstruction [8]. The same authors suggest that this surgical calculator can be improved by the inclusion of several factors important for risk stratification in head and neck oncology, namely, the performance of free flap reconstruction. Furthermore, other study concluded that ACS-NSQIP calculator may be insufficiently calibrated to accurately predict postoperative complication risk for patients previously exposed to chemoradiation undergoing salvage laryngectomy [32]. The same authors, advised caution when estimating postoperative risk among patients undergoing salvage procedures, especially those of older age, poorer functional status, and those requiring neck dissection [32]. There is increasing recognition of the importance of a specialty-specific ACS-NSQIP and were many the studies proving that this scale is currently inadequate for head and neck surgery. Indeed, efforts to develop

disease- and procedure-specific preoperative, intraoperative, and postoperative variables specific to head and neck surgery have been undertaken [8, 32]. We agree with other authors who state that an essential first step in mitigating the inaccuracy of ACS-NSQIP for head and neck procedures, is the combination of CPT codes [28]. In fact, many of the operations performed included multiple high-risk procedures done concurrently, and the final CPT code attributed was not truly representative of the actual complexity of each surgery.

Our study demonstrated that the ARISCAT score was a reliable risk calculator for predicting postoperative respiratory complications. Other studies had conflicting results regarding the value of ARISCAT scale in head and neck patients. Wood et al. observed poor predictive performance of ARISCAT in a cohort of 794 patients admitted for major head and neck surgery at their institution [33]. These discrepancies in the literature concerning the accuracy of ARISCAT scale in head and neck patients might be explained by a number of factors. First, the ARISCAT score was validated in a large surgical population in which a very reduced fraction were head and neck surgeries. In addition, the variable "surgical site" is not as important for major head and neck surgery as it is for other surgical specialities where chest wall and diaphragm manipulation might occur and significantly contribute to the risk of postoperative pulmonary complications. Furthermore, the distortion of the upper airway, the frequent use of tracheostomy or surgical resections that might alter the upper aerodigestive anatomy and imply the potential risk for aspiration are unique features in this subgroup of patients [33]. Nevertheless, we consider that ARISCAT score might useful to stratify risk when advising patients before surgery and, to identify patients most likely to benefit from risk-reduction interventions.

We managed to design a new risk tool for our institution which better predicts the risk of serious complications in our patients. It should be emphasized that apparently modest predictive values for the risk scores and for our regression model that would not be acceptable in diagnostic tests, where accuracy is essential, may still be very helpful in prognostic models, which are used in preoperative visits to predict a complication risk higher than average. Therefore, these results allow us to define our model as a tool with moderate to good clinical utility to estimate the risk of complications. Our next goal is to implement prehabilitation programmes, including its four dimensions, in our high-risk patients undergoing major head and neck surgery.

There are several limitations to this study worthy of discussion. First, it is a retrospective study with a low population number from a single institution. Secondly, we have used general surgical risk calculators which are not yet adapted to head and neck procedures. Other important limitation to mention is that our final model was developed from the compilation of other risk models already existent which results in a high number of variables to be collected and computed. Nevertheless, we have a created a validated risk tool adapted to our population which successfully selects high-risk patients who may require additional care to preempt complications or to resolve them after they occur.

Further research is needed to understand whether additional patient attributes should be supplemented in the calculator to improve its predictive value.

Despite all that has been said, and recognizing the valuable benefits of the risk tools we have analysed, risk prediction models cannot take into account subtleties in patients, their diseases or the technical difficulties of every single operation, the individual performance of the surgeon and the fulfilment of good care standards of every institution. Therefore, whenever necessary, clinical judgment should override any predicted outcome of any risk scales.

Author contributions ASM and LLS designed the study. AF, CS and ASM collected and analysed the data. ASM takes full responsibility for the integrity of the data presented. All authors contributed to the analysis and interpretation of the data for the work. JR, LA and FM made valuable contributions to the statistical analysis. EM and LLS were also responsible for the study supervision. ASM was responsible for the drafting of the manuscript and all the authors for revising it for important intellectual content.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. This study was approved by the Ethical Committee of our institution.

Appendices

Appendix A- The American Society of Anesthesiologists physical status

ASA I	Normal healthy patient
ASA II	Patients with mild systemic disease

ASA III	Patients with severe systemic disease
ASA IV	Patients with severe systemic disease that is a constant threat to life
ASA V	Moribund patients who are not expected to survive without the operation
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes

Appendix B- P-POSSUM SCORE

Physiologic score	Operative score
Age (Years)	Operative severity Score
Cardiac signs	Multiple procedures
Respiratory history	Total blood loss
Systolic blood pressure (mm Hg)	Peritoneal soiling
Pulse (beats/min)	Presence of malignancy
Glasgow coma score	Mode of surgery
Haemoglobin g/dL)	
White cell count ($\times 10^{12}$/L	
Urea (mg/dL)	
Sodium (mmol/L)	
Potassium (mmol/L)	
Electrocardiogram	

Appendix C- *ACS NSQIP risk calculator*

Preoperative patient and surgical inputs	NSQIP risk outcomes
Age group	Serious complication
Sex	Any complication
Functional status	Pneumonia
Emergency case	Cardiac complication
ASA class	Surgical site infection
Wound class contamination	Urinary tract Infection
Steroid use for chronic condition	Venous thromboembolism
Ascites within 30 days prior to surgery	Renal failure
Systemic sepsis within 48 h prior to surgery	Readmission
Ventilator dependent	Return to OR
Disseminated cancer	Death
Diabetes	Discharge to nursing or Rehab facility
Hypertension requiring medication	Predicted length of hospital stay
Preoperative patient and surgical inputs	NSQIP risk outcomes
Congestive heart failure in 30 days prior to surgery	
Dyspnea	
Current smoker within 1 year	
History of severe COPD	
Dialysis	
Acute renal failure	
Body mass index calculation (weight and height)	

Appendix D—The seven ariscat risk predictors

1. Age (year) (≤ 50; 51–80, > 80 year)
2. Preoperative Spo2 (≥ 96, 91–95%, ≤ 90%)
3. Respiratory infection in the last month
4. Preoperative anemia (Hb ≤ 10 g/dl)
5. Surgical incision (Peripheral; upper abdominal, intrathoracic)
6. Duration of surgery (h)
7. Emergency procedure

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5.2 Anexo II: Trabalho original não integrado na investigação nuclear do ciclo de doutoramento, porém com ele relacionado, citado no capitulo de discussão, conclusões e trabalhos futuros

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; et al
eAPPENDIX 1 NATIONAL COORDINATORS: Portugal: **Antero do Vale Fernandes**
JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291
PMID: 26903337, Fator de impacto: 47,7

Importância: As informações sobre a epidemiologia, reconhecimento, gestão, e desfechos de doentes com síndrome de Distress Respiratório Agudo (ARDS) são ainda limitadas.
Objetivos: Avaliar a incidência e o desfecho do ARDS em unidade de cuidados intensivos (UCI) e avaliar o seu reconhecimento clínico, gestão da ventilação mecânica, uso de adjuvantes, como por exemplo o decúbito ventral na prática clínica de rotina para doentes com critérios de ARDS segundo a definição de Berlim.
Projeto, ajuste e participantes: Estudo internacional, de coorte prospetivo, multicêntrico observacional amplo, com o obejtivo de compreender o Impacto global da Insuficiência Respiratória Aguda Grave (LUNG SAFE), submetidos a procedimentos invasivos ou não invasivos. A ventilação mecânica foi monitorizada, durante 4 semanas consecutivas. Participaram 459 UCIs de 50 países em 5 continentes.
Principais resultados e medidas: O outcome primário foi a incidência de ARDS na UCI, e os outcomes secundários incluíram a avaliação do reconhecimento clínico do ARDS, a gestão da ventilação mecânica, o uso de intervenções adjuvantes na prática clínica de rotina, e os resultados clínicos do ARDS..

Resultados: Dos 29.144 pacientes admitidos nas UCIs participantes, 3.022 (10,4%) preencheram criterios de ARDS. Destes, 2.377 doentes desenvolveram ARDS nas primeiras 48 horas e a insuficiência respiratória foi tratada com ventilação mecânica invasiva. A prevalência de ARDS leve foi de 30,0% (IC 95%, 28,2% -31,9%); de ARDS moderado, 46,6% (IC 95%, 44,5% -48,6%); e ARDS grave, 23,4% (IC 95%, 21,7% -25,2%). O ARDS representou 0,42 casos por cama de UCI durante 4 semanas e representou 10,4% (IC 95%, 10,0% -10,7%) das admissões na UCI e 23,4% dos doentes que necessitam de ventilação mecânica. O reconhecimento clínico de ARDS variou de 51,3% (IC de 95%, 47,5% -55,0%) em leve a 78,5% (IC de 95%, 74,8% -81,8%) no ARDS grave. Menos de dois terços dos doentes com ARDS receberam um volume corrente de 8 mL / kg de peso corporal previsto. A pressão de platô foi medida em 40,1% (95% CI, 38,2-42,1), enquanto 82,6% (95% CI, 81,0% -84,1%) receberam uma pressão positiva expositiva final (PEEP) inferior a 12 cm H_2O.

O decúbito ventral foi usado em 16,3% (IC 95%, 13,7% -19,2%) dos doentes com ARDS grave.

O reconhecimento clínico de ARDS foi associado a maior PEEP, maior uso de bloqueio neuromuscular e decúbito ventral. A mortalidade hospitalar foi de 34,9% (IC de 95%, 31,4% -38,5%) para os doentes com ARDS leve, 40,3% (95% CI, 37,4% -43,3%) ARDS moderado, e 46,1% (95% CI, 41,9% -50,4%) para ARDS grave.

Conclusões e relevância: Nas UCIs dos 50 países estudados, o período de prevalência de ARDS foi de 10,4% das admissões. Esta síndrome foi sub-reconhecida, subtratada e associou-se a uma elevada taxa de mortalidade. Esses achados traduzem grande potencial de melhoria no manejo de doentes com ARDS.

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Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

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IMPORTANCE Limited information exists about the epidemiology, recognition, management, and outcomes of patients with the acute respiratory distress syndrome (ARDS).

OBJECTIVES To evaluate intensive care unit (ICU) incidence and outcome of ARDS and to assess clinician recognition, ventilation management, and use of adjuncts—for example prone positioning—in routine clinical practice for patients fulfilling the ARDS Berlin Definition.

DESIGN, SETTING, AND PARTICIPANTS The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) was an international, multicenter, prospective cohort study of patients undergoing invasive or noninvasive ventilation, conducted during 4 consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across 5 continents.

EXPOSURES Acute respiratory distress syndrome.

MAIN OUTCOMES AND MEASURES The primary outcome was ICU incidence of ARDS. Secondary outcomes included assessment of clinician recognition of ARDS, the application of ventilatory management, the use of adjunctive interventions in routine clinical practice, and clinical outcomes from ARDS.

RESULTS Of 29 144 patients admitted to participating ICUs, 3022 (10.4%) fulfilled ARDS criteria. Of these, 2377 patients developed ARDS in the first 48 hours and whose respiratory failure was managed with invasive mechanical ventilation. The period prevalence of mild ARDS was 30.0% (95% CI, 28.2%-31.9%); of moderate ARDS, 46.6% (95% CI, 44.5%-48.6%); and of severe ARDS, 23.4% (95% CI, 21.7%-25.2%). ARDS represented 0.42 cases per ICU bed over 4 weeks and represented 10.4% (95% CI, 10.0%-10.7%) of ICU admissions and 23.4% of patients requiring mechanical ventilation. Clinical recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) in mild to 78.5% (95% CI, 74.8%-81.8%) in severe ARDS. Less than two-thirds of patients with ARDS received a tidal volume 8 of mL/kg or less of predicted body weight. Plateau pressure was measured in 40.1% (95% CI, 38.2-42.1), whereas 82.6% (95% CI, 81.0%-84.1%) received a positive end-expository pressure (PEEP) of less than 12 cm H_2O. Prone positioning was used in 16.3% (95% CI, 13.7%-19.2%) of patients with severe ARDS. Clinician recognition of ARDS was associated with higher PEEP, greater use of neuromuscular blockade, and prone positioning. Hospital mortality was 34.9% (95% CI, 31.4%-38.5%) for those with mild, 40.3% (95% CI, 37.4%-43.3%) for those with moderate, and 46.1% (95% CI, 41.9%-50.4%) for those with severe ARDS.

CONCLUSIONS AND RELEVANCE Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized and undertreated and associated with a high mortality rate. These findings indicate the potential for improvement in the management of patients with ARDS.

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Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury, associated with increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue.[1] Although prior epidemiologic studies have provided substantial insights into ARDS,[2-5] there remains limited information about the epidemiology, recognition, management, and outcomes of patients with the ARDS, especially in the era of the current Berlin Definition.[1] This definition was constructed empirically and validated using retrospective cohorts[1]; however, prospective studies of the Berlin Definition have been limited to small numbers of centers and patients.[6,7]

We set out to address some clinically important questions regarding ARDS. The current incidence and mortality of ARDS in a large international cohort is not known. Large regional differences have been suggested; for example, the incidence of ARDS in Europe[5] is reported to be 10-fold lower than in the United States.[4] A number of ventilatory interventions, such as lower tidal volumes,[8] higher positive end-expiratory pressure (PEEP),[9] and adjuncts such as prone positioning,[10] neuromuscular blockade,[11] and extracorporeal membrane oxygenation[12] for ARDS have been proposed. It is not clear how these interventions are applied in routine practice in the broader international context. Implementation of effective therapies may be limited by lack of recognition of ARDS by clinicians.[13,14] Understanding the factors associated with ARDS recognition and its effect on management could lead to effective interventions to improve care.

Therefore, we undertook the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) to determine the intensive care unit (ICU) epidemiology and outcomes from ARDS, assess clinician recognition of ARDS, and understand how clinicians use mechanical ventilation and adjunctive interventions in routine clinical practice.

Methods

Study Design

This study was an international, multicenter, prospective cohort study. The enrollment window consisted of 4 consecutive winter weeks (February-March 2014 in the Northern hemisphere and June-August 2014 in the Southern hemisphere), as selected by each ICU. We aimed to recruit a broadly representative sample of ICUs by public announcements by the European Society of Intensive Care Medicine, by national societies and networks endorsing the study, and by designated national coordinators (eAppendix 1 in the Supplement). The study ICUs represent a convenience sample of those that agreed to participate in the study and had enrolled at least 1 patient. Different ICUs from the same hospital were considered as separate centers; each ICU provided baseline data concerning its resources (eTable 1 in the Supplement). All participating ICUs obtained ethics committee approval and obtained either patient consent or ethics committee waiver of consent. We recruited physicians from each participating country as lead site investigators and national coordinators. Site investigators (eAppendix 2 in the Supplement) were also responsible for ensuring data integrity and validity, and were offered web-based training to enhance chest x-ray interpretation reliability as part of a substudy.

Patients, Study Design, and Data Collection

All patients, including ICU transfers, admitted to an ICU within the 4-week enrollment window and receiving invasive or noninvasive ventilation were enrolled. Exclusion criteria were age younger than 16 years or inability to obtain informed consent, when required. Following enrollment, patients were evaluated daily for acute hypoxemic respiratory failure, defined as the concurrent presence of (1) ratio of arterial oxygen tension to inspired fraction of oxygen (Pao_2/Fio_2) of 300 mm Hg or less; (2) new pulmonary parenchymal abnormalities on chest x-ray or computed tomography; and (3) ventilatory support with continuous positive airway pressure (CPAP), expiratory positive airway pressure (EPAP), or positive end-expiratory pressure (PEEP) of 5 cm H_2O or more

Day 1 was defined as the first day that acute hypoxemic respiratory failure criteria were satisfied, irrespective of ICU admission date. The case report form (eAppendix 3 in the Supplement) automatically prompted investigators to provide an expanded data set for days 1, 2, 3, 5, 7, 10, 14, 21, and 28 or at ICU discharge or death. All data were recorded at the same time, normally as close as possible to 10 AM each day. Patient outcomes included date of liberation from mechanical ventilation and vital status at ICU discharge and at either hospital discharge or at day 90, whichever occurred earlier.

Quality Control

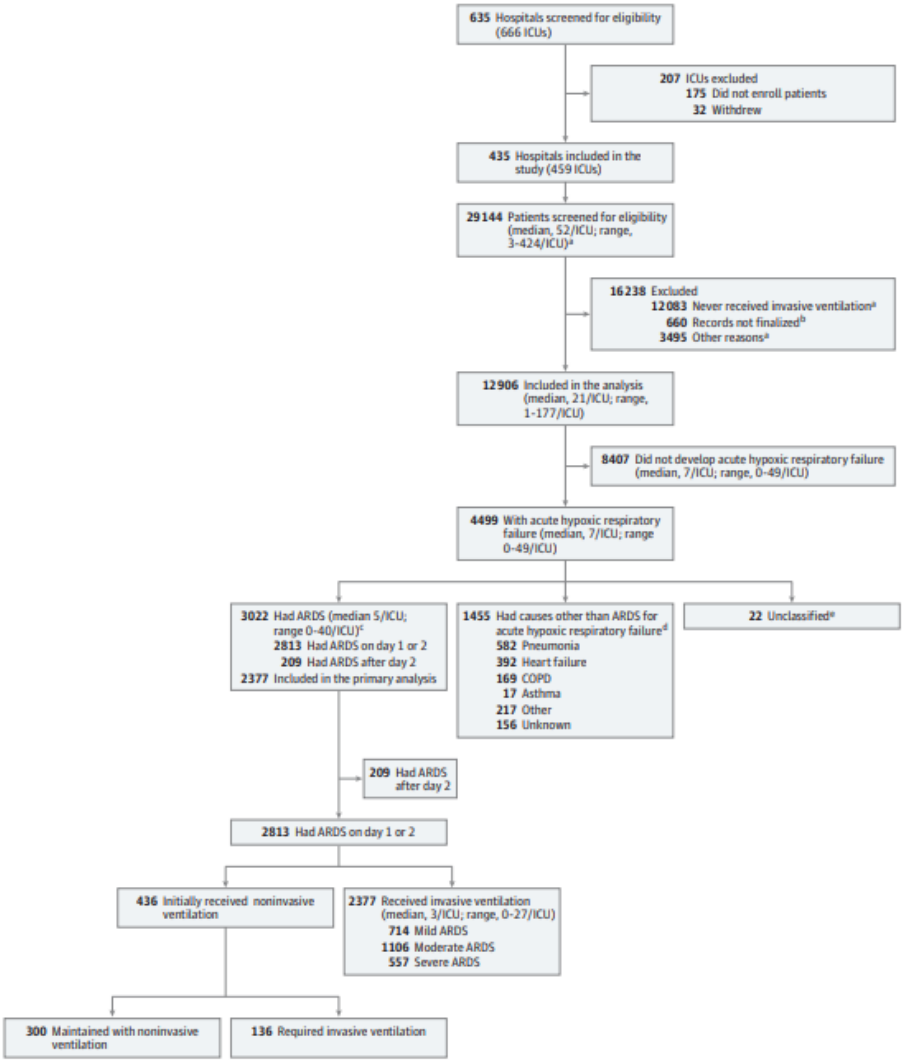
At the time of data entry, the site investigators were required to answer all queries raised by the case report form before they could electronically finalize a patient data set. Patient data sets that were not finalized were not included in the analysis (**Figure 1**). In addition, prior to analysis, all data were screened for potentially erroneous data and outliers. These data were verified or corrected by site investigators. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for observational cohort studies.[15]

Identification and Recognition of ARDS

The diagnosis of ARDS was made by a computer algorithm in the analysis phase of the study using the raw data that made up the various components of the Berlin ARDS Definition: (1) presence of acute hypoxemic respiratory failure criteria, (2) onset within 1 week of insult, or new (within 7 days) or worsening respiratory symptoms; (3) bilateral airspace disease on chest x-ray or computed tomography not fully explained by effusions, lobar or lung collapse, or nodules; and (4) cardiac failure not the primary cause of acute hypoxemic respiratory failure.

We assessed clinician recognition of ARDS at 2 time points. On day 1 of study entry, site investigators indicated the reasons for the patient's hypoxemia, with ARDS included as a potential cause. If the answer was "yes," ARDS was deemed to have been clinician-recognized on day 1. When patients exited the study, investigators were asked if the patient had ARDS at any stage during their ICU stay. ARDS was deemed to have

Figure 1. Flow of Patient Screening and Enrollment



[a] Projected from data provided by 360 intensive care units (ICUs [78%]). Data specifying other reasons were not collected during the study.

[b] Patient electronic case report forms that were not fully complete were excluded.

[c] Number included in the primary analysis.

[d] Patients could have more than one cause for acute hypoxic respiratory failure.

[e] For unclassified patients it was not possible to determine whether they fulfilled the criteria for acute respiratory distress syndrome (ARDS) due to incomplete data.

obstructive pulmonary disease, pneumonia, etc were left to clinician discretion.

ARDS Severity and Mechanical Ventilation Parameters

Patients with ARDS undergoing invasive ventilation were categorized on the day of ARDS diagnosis based on their Pao_2/Fio_2 ratio into mild (200 <Pao_2/Fio_2 ≤300 mm Hg), moderate (100 <Pao_2/Fio_2 ≤200 mm Hg), and severe (Pao_2/Fio_2 <100 mm Hg) based on the Berlin Definition.[1] Given the lack of clarity in the Berlin Definition regarding the severity classification of patients managed with noninvasive ventilation, and the difficulty in comparing noninvasive ventilation settings to invasive modes, we excluded patients ventilated on noninvasive ventilation from the analyses pertaining to severity, ventilator management or outcome. To ensure a more homogenous data set, we restricted subsequent analyses to the large subset of patients (93.1%) fulfilling ARDS criteria on day 1 or 2 from onset of acute hypoxemic respiratory failure.

Invasive ventilator-free days were calculated as the number of days from weaning from invasive ventilation to day 28. Patients who died before weaning were considered to have a ventilator-free-day value of 0. Driving pressure was defined as plateau pressure (P_{plat}) minus PEEP.

Patients were considered to have no evidence for spontaneous ventilation when set and measured respiratory rates were equal.

Calculation of Period Prevalence and Per-ICU-Bed ARDS Incidence

The period prevalence of patients with ARDS was calculated by dividing the number of patients fulfilling ARDS criteria by the total number of patients admitted to the ICU in the 28-day study period (ie, 29 160). The number of patients with ARDS per ICU bed over the 4-week study period was calculated as number of patients with ARDS/number of ICU beds available.

ICU Enrollment and Statistical Analysis

The primary outcome was to determine the ICU incidence of ARDS. Secondary outcomes included assessment of clinician recognition of ARDS, the application of ventilatory management, the use of adjunctive interventions in routine clinical practice, and the outcomes from ARDS. We wished to enroll at least 1000 patients with ARDS. Assuming a 30% mortality, 300 deaths would allow us to evaluate at least 30 associated variables in multivariable models.[16] Prior epidemiological studies reported an ARDS incidence ranging between 2.2% and 19% of ICU patients.[2-5] Based on a conservative a priori estimate that 5% of ICU admissions would have ARDS and projecting that a medium-sized ICU admits 50 patients per month, we planned to enroll at least 500 ICUs worldwide.

Descriptive statistics included proportions for categorical and mean (standard deviation) or median (interquartile range [IQR]) for continuous variables. The amount of missing data was low, with the exception of plateau pressure P_{plat} and arterial oxygen saturation (Sao_2), and is detailed in eTable 2 in the Supplement). No assumptions were made for missing data. Data were unadjusted unless specifically stated otherwise. Proportions were compared using χ^2 or Fisher exact tests and continuous variables were compared using the *t* test or Wilcoxon rank-sum test, as appropriate. To evaluate variables associated with clinician recognition of ARDS, covariates determined a priori to be associated with ARDS recognition and covariates associated with ARDS recognition with $P < .20$ in bivariate analyses were entered into multivariable regression models with variable selection based on a stepwise backward elimination pro-

Table 1. Characteristics of Patients With Acute Respiratory Distress Syndrome

Parameter	Value
No. of patients	
ARDS	3022
ARDS in first 48 h after AHRF	2813
No longer fulfill ARDS criteria after 24 h, No. (%) [95% CI]	486 (17) [15.9-18.7]
Clinician recognition of ARDS, No. (%) [95% CI]	1820 (60) [59-62.0]
Age, mean (95% CI)y	61.5 (60.9-62.1)
Women, No. (%)	1151 (38)
Height, mean (95% CI), cm	168 (167.6-168.4)
Weight, mean (95% CI), kg	78.0 (77-79)
Chronic disease, No. (%)	
COPD	657 (21.7)
Diabetes	657 (21.7)
Immunoincompetence	365 (12.1)
Chronic cardiac failure	314 (10.4)
Chronic renal failure	306 (10.1)
Active neoplasm	258 (8.5)
Hematological disease	142 (4.7)
Risk factor for ARDS, No. (%)[a]	
Pneumonia	1794 (59.4)
Extrapulmonary sepsis	484 (16.0)
Aspiration	430 (14.2)
Noncardiogenic shock	226 (7.5)
Trauma	127 (4.2)
Blood transfusion	118 (3.9)
Pulmonary contusion	97 (3.2)
Inhalation	72 (2.3)
Drug overdose	56 (1.9)
Pulmonary vasculitis	41 (1.4)
Burn	9 (0.3)
Drowning	2 (0.1)
Other risk factor	82 (2.7)
No risk factor	252 (8.3)
Duration of invasive mechanical ventilation, median (IQR), d	8 (4-16)
Duration of ICU stay, median (IQR), d	10 (5-19)
ICU survival, No. (%) [95% CI]	1994 (66.0) [64.3-67.7]
Duration of hospital stay, median (IQR), d	17 (9-32)
Hospital survival, No. (%) [95% CI][b]	1826 (60.4) [58.7-62.2]

Abbreviations: AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR (interquartile range).

[a] Total is greater than 100%, because patients could have more than 1 risk factor.

[b] Data are missing for 10 patients.

Table 2. Organizational and Patient Factors Associated With Clinician Recognition of ARDS in Invasively Ventilated Patients

	ARDS Recognized, No./Total No. (%)	Absolute Difference (95% CI)	Bivariate OR (95% CI)	*P* Value[a]	Multivariable OR (95% CI)	*P* Value[b]
No. of patients/staff physician, for each additional patient		−1.20 (−0.74 to −1.66)[c]	0.960 (0.945 to 0.976)	<.001	0.959 (0.942 to 0.977)	<.001
No. of patients/nurse, for each additional patient		−0.34 (−0.55 to −0.13)[c]	0.911 (0.860 to 0.957)	<.001	0.920 (0.870 to 0.968)	.002
Age, per year		−4.03 (−5.43 to −2.65)[c]	0.985 (0.980 to 0.990)	<.001	0.987 (0.980 to 0.993)	<.001
Predicted body weight per kg		−1.27 (−2.18 to −0.36)[c]	0.989 (0.980 to 0.997)	.006	0.984 (0.974 to 0.993)	<.001
Nonpulmonary SOFA per point		0.81 (0.48 to 1.12)[c]	1.054 (1.031 to 1.077)	<.001	1.057 (1.030 to 1.085)	<.001
Pao_2:Fio_2 ratio, per mm Hg		−30.0 (−35.5 to −24.4)[c]	0.993 (0.992 to 0.995)	<.001	0.993 (0.992 to 0.995)	<.001
Medical or surgical Admission with trauma						
No	1477/2274 (65.0)		1 [Reference]		1 [Reference]	
Yes	48/103 (46.6)	−18.4 (−28.7 to −8.0)	0.471 (0.316 to 0.700)	<0.001	0.539 (0.334 to 0.868)	.011
Neoplastic or immune or hematologic disease						
No	1173/1892 (62.0)		1 [Reference]		1 [Reference]	
Yes	352/485 (72.6)	10.6 (6.0 to 15.1)	1.623 (1.305 to 2.027)	<.001	1.396 (1.079 to 1.816)	.012
Pneumonia						
No	440/1002 (43.9)		1 [Reference]		1 [Reference]	
Yes	963/1375 (70.0)	26.1 (22.2 to 30.0)	1.830 (1.544 to 2.170)	<.001	1.339 (1.073 to 1.670)	.01
Pancreatitis						
No	844/2328 (36.3)		1 [Reference]		1 [Reference]	
Yes	41/49 (83.7)	47.4 (36.9 to 58.0)	2.915 (1.436 to 6.733)	.006	3.506 (1.439 to 10.543)	.01
ARDS risk factors						
Yes	1454/2187 (66.5)		1 [Reference]		1 [Reference]	
No	71/190 (37.4)	−29.1 (−36.3 to −22.0)	0.301 (0.220 to 0.408)	<.001	0.408 (0.280 to 0.591)	<.001
With heart failure						
No	1347/2027 (66.5)		1 [Reference]		1 [Reference]	
Yes	178/350 (50.9)	−15.6 (−21.2 to −10.0)	0.522 (0.415 to 0.657)	<.001	0.496 (0.377 to 0.652)	<.001

Abbreviations. ARDS, acute respiratory distress syndrome; $Pao_2/Fio2$; partial pressure of oxygen to fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

[a] Bivariate analysis.

[b] All variables included in the multivariable analysis are reported in this Table.

[c] These values are the mean difference (95% CI).

cedure using *P* values. The association of clinician recognition with ventilatory management of ARDS was determined for tidal volume, PEEP, P_{plat} measurement, and use of prone positioning and neuromuscular blockade in separate multivariable stepwise backward logistic or multiple linear regression models as appropriate. We did not perform any longitudinal data analyses. A Kaplan-Meier estimate of the cumulative probability of unassisted breathing and survival to day 28 was performed. Patients discharged from the hospital before day 28 were assumed alive at this time point. Statistical analyses were performed with R 3.2.3 (http://www.R-project.org). All *P* values were 2-sided, with *P* values <.05 considered statistically significant. The study protocol, case report form and full statistical analysis plan are included in eAppendix 3 in the Supplement.

Results

Participating ICUs and Patients Enrolled

Six hundred sixty-six ICUs registered for the study. Following data verification and elimination of nonrecruiting sites, 459 ICUs from 50 countries were included in the final analysis (eTable 1 and eTable 3 in the Supplement). Of the 29 144 patients admitted to these ICUs during the enrollment period, 13 566 patients receiving ventilatory support were enrolled. Complete data sets from 12 906 patients were analyzed (Figure 1). **Table 1** outlines their key characteristics.

Characteristics of Patients Enrolled

Of 4499 patients with acute hypoxemic respiratory failure, 3022 (67.2%) fulfilled ARDS criteria during their ICU stay. Of these, 2813 (93.1%) developed ARDS at day 1 (n = 2665) or day 2 (n = 148), whereas 209 patients (6.9%) developed ARDS after day 2 of acute hypoxemic respiratory failure (Figure 1). The 436 patients (14.4%) with ARDS who received noninvasive ventilation were excluded from analyses regarding ARDS severity, mechanical ventilation settings, and outcome.

ICU Incidence of ARDS

ARDS represented 10.4% (95% CI, 10.0%-10.7%) of total ICU admissions and 23.4% (95% CI, 21.7%-25.2%)of all patients requiring mechanical ventilation and constituted 0.42 cases/ICU bed over 4 weeks. There was some geographic variation, with Europe having an incidence of 0.48 cases/ICU bed over 4 weeks; North America, 0.46; South America, 0.31; Asia, 0.27; Africa, 0.32; and Oceania, 0.57 cases/ICU bed per 4 weeks.

Table 3. Baseline Characteristics of Patients With Acute Respiratory Distress Syndrome Treated With Invasive Ventilation by Severity Category at Diagnosis

Parameter	All (N = 2377)	Mild (n = 714)	Moderate (n = 1106)	Severe (n = 557)	P Value[a]
Age, median (IQR), y	61 (61-62)	61 (60-63)	62 (62-63)	57 (55-58)	<.001
No longer meet ARDS criteria after 24 h, No. (%) [95% CI]	486 (17.3) [15.9-18.7]	190 (26.6) [23.4-30.0]	152 (13.7) [11.8-15.9]	71 (12.8) [10.1-15.8]	<.001
Severity of illness, mean (95% CI), SOFA score[b]					
Day 1	10.1 (9.9-10.2)	8.8 (8.6-9.1)	10.2 (9.9-10.4)	11.4 (11.1-11.8)	<.001
Day 1 nonpulmonary[c]	6.9 (6.7-7.0)	6.7 (6.4-7.0)	6.9 (6.7-7.1)	7.0 (6.7-7.4)	.34
Worst	11.1 (10.9-11.3)	10.3 (10.0-10.6)	11.8 (11.5-12.0)	13.0 (12.6-13.3)	<.001
Worst nonpulmonary	8.0 (7.8-8.2)	8.0 (7.7-8.3)	8.7 (8.4-8.9)	9.0 (8.4-8.9)	<.001
Ventilator settings, first day of ARDS					
F_{IO_2}, mean (95% CI)	0.65 (0.64-0.65)	0.48 (0.47-0.50)	0.62 (0.61-0.63)	0.90 (0.88-0.91)	<.001
Median (IQR)	0.6 (0.45-0.85)	0.4 (0.4-0.5)	0.6 (0.5-0.7)	1 (0.8-1)	
Set respiratory rate, mean (95% CI), 1/min	18.6 (18.3-19.0)	17.4 (16.9-17.8	18.4 (18.0-18.5)	20.4 (19.2-21.6)	<.001
Total respiratory rate, mean (95% CI), 1/min	20.8 (21.5-21.2)	19.5 (19.0-19.9)	20.7 (20.3-21.1)	22.7 (21.5-23.8)	<.001
VT, mean (95% CI), mL/kg PBW	7.6 (7.5-7.7)	7.8 (7.6-7.9	7.6 (7.5-7.7)	7.5 (7.3-7.6)	.02
Control vent mode	7.5 (7.4-7.6)	7.6 (7.5-7.8)	7.4 (7.3-7.6)	7.4 (7.2-7.6)	.06
Spontaneous vent mode	7.9 (7.8-8.1)	7.9 (7.7-8.2)	8.0 (7.7-8.2)	7.7 (7.4-8.1)	.55
P value (control vs spont mode)	<.001	.049	<.001	.053	
Set PEEP, mean (95% CI), cm H_2O	8.4 (8.3-8.6)	7.4 (7.2-7.6)	8.3 (8.1-8.5)	10.1 (9.8-10.4)	<.001
Peak pressure, mean (95% CI), cm H_2O[d]	27.0 (26.7-27.4)	24.7 (24.1-25.4)	26.9 (26.5-27.4)	30.3 (29.6-30.9)	<.001
Patients in whom P_{PLAT} measured, No. (%)					
Among all invasively ventilated patients, No. (%) [95% CI]	954 (40.1) [38.2-42.1]	260 (36.4) [32.9-40.1]	463 (41.9) [38.9-44.8]	231 (41.5) [37.3-45.7]	.05
Among patients with controlled ventilation, No. (%) [95% CI]	756 (48.5) [46.0-51.0]	198 (46.1) [41.3-51.0]	363 (49.8) [46.1-53.5]	195 (48.5) [43.5-53.5]	.49
P_{PLAT}, mean (95% CI), cm H_2O[e]	23.2 (22.6-23.7)	20.5 (19.8-21.3)	23.1 (22.6-23.7)	26.2 (25.2-27.1)	<.001
Standardized minute ventilation, mean (95% CI), l/min[f]	10.8 (10.6-11.0)	9.3 (9.1-9.6)	10.7 (10.5-11.0)	12.8 (12.3-13.3)	<.001
Spontaneous ventilation, No. (%) [95% CI]	723 (30.4 [8.6-32.3]	260 (36.4) [32.9-40.0]	336 (30.4) [29.7-35.3]	127 (22.8) [19.3-26.5]	<.001
Gas exchange, first day of ARDS					
Pao_2/F_{IO_2} ratio, mean (95% CI), mmHg	161 (158-163)	246 (244-248)	149 (147-150)	75 (74-77)	<.001
SpO_2, mean (95% CI)	95 (94-95)	97 (97-98)	95 (95-96)	90 (89-91)	<.001
Median (IQR)	96 (93-98)	98 (96-99)	96 (94-98)	92 (88-95)	
$Paco_2$, mean (95% CI), mm Hg	46.0 (45.4-46.6)	41.5 (40.7-42.2)	45.8 (44.9-46.6)	52.2 (50.7-53.7)	<.001
pH, mean (95% CI)	7.33 (7.32-7.33)	7.36 (7.36-7.37)	7.33 (7.32-7.33)	7.27 (7.26-7.29)	<.001

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Pao_2/F_{IO_2}, partial pressure of oxygen to fraction of inspired oxygen; P_{PLAT}, plateau pressure; SOFA, Sequential Organ Failure Assessment; VT, tidal volume; Spo_2, peripheral arterial oxygen saturation.

[a] *P* value represents comparisons across the ARDS severity categories for each variable.

[b] For all SOFA scores for which data points were missing, this value was omitted and the denominator adjusted accordingly.

[c] The nonpulmonary SOFA score and the pulmonary component of the score was omitted and the denominator adjusted accordingly.

[d] For peak pressure measurements, patients receiving high-frequency oscillatory ventilation (HFOV) or extracorporeal membrane oxygenation (ECMO) were excluded.

[e] Plateau pressure values are limited to patients in whom this value was reported and in whom either an assist control mode was used or in whom a mode permitting spontaneous ventilation was used. The set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

[f] Standardized minute ventilation = minute ventilation × $Paco_2$/40 mm Hg.

Recognition of ARDS

ARDS was underdiagnosed, with 60.2% of all patients with ARDS being clinician-recognized. Clinician recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) for mild ARDS to 78.5% (95% CI, 74.8%-81.8%) for severe ARDS (eTable 4 in the Supplement). Clinician recognition of ARDS at the time of fulfillment of ARDS criteria was 34.0% (95% CI, 32.0-36.0), suggesting that diagnosis of ARDS was frequently delayed.

A multivariable analysis including variables from the bivariable analyses (eTable 5 in the Supplement), revealed several patient and organizational factors associated with clinician recognition of ARDS. Higher nurse-to-patient ratios, higher physician-to-patient ratios, younger patient age and a lower Pao_2/F_{IO_2} ratio, and the presence of pneumonia or pancreatitis were factors independently associated with higher probability of clinician recognition (**Table 2**). Absence of a risk factor and presence of concomitant

Table 4. Use of Adjunctive and Other Optimization Measures in Invasively Ventilated Patients With Acute Respiratory Distress Syndrome[a]

	Patients of No. (%) [95% CI]				
	All (n = 2377)	Mild[a] (n = 498)	Moderate[a] (n = 1150)	Severe[a] (n = 729)	P Value[b]
Neuromuscular blockade	516 (21.7) [20.1-23.4]	34 (6.8) [4.8-9.4]	208 (18.1) [15.9-20.4]	274 (37.8) [34.1-41.2]	<.001
Recruitment maneuvers	496 (20.9) [19.2-22.6]	58 (11.7) [9.0-14.8]	200 (17.4) [15.2-19.7]	238 (32.7) [29.3-36.2]	<.001
Prone positioning	187 (7.9) [6.8-9.0]	5 (1.0) [0.3-2.3]	63 (5.5) [4.2-7.0]	119 (16.3) [13.7-19.2]	<.001
ECMO	76 (3.2) [2.5-4.0]	1 (0.2) [0.05-1.2]	27 (2.4) [1.6-3.4]	48 (6.6) [4.9-8.6]	<.001
Inhaled vasodilators	182 (7.7) [6.6-8.8]	17 (3.4) [02.0-5.4]	70 (6.1) [4.8-7.6]	95 (13.0) [10.7-15.7]	<.001
HFOV	28 (1.2) [0.8-1.7]	3 (0.6) [0.1-1.7]	14 (1.2) [0.7-2.0]	11 (1.5) [0.8-2.7]	.347
None of the above	1431 (60.2) [58.2-62.2]	397 (79.7) [75.9-83.2]	750 (65.2) [62.4-68.0]	284 (39.0) [35.4-42.6]	<.001
Esophageal pressure catheter	19 (0.8) [0.04-1.4]	2 (0.4) [0.04-1.4]	8 (0.7) [0.3-1.3]	9 (1.2) [0.6-2.3]	.233
Tracheostomy	309 (13.0) [11.6-14.4]	48 (9.6) [7.1-12.6]	155 (13.5) [11.6-15.6]	106 (14.5) [12.1-17.3]	.034
High-dose corticosteroids[c]	425 (17.9) [16.4-19.5]	61 (12.3) [9.5-15.5]	194 (16.9) [14.7-19.2]	170 (23.3) [20.3-26.6]	<.001
Pulmonary artery catheter	107 (4.5) [3.7-5.4]	9 (1.8) [0.8-3.4]	53 (4.6) [3.4-6.0]	45 (6.2) [4.5-8.2]	.001

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; PEEP, positive end-expiratory pressure.

[a] For this analysis, ARDS severity was defined based on the patients' worst severity category over the course of their ICU stay in patients who developed ARDS on day 1 or 2.

[b] P value represents comparisons across the ARDS severity categories for each variable.

[c] High-dose corticosteroids was defined as doses that were equal to or greater than the equivalent of 1 mg/kg of methylprednisolone.

Table 5. Outcome of Invasively Ventilated Patients by Acute Respiratory Distress Syndrome Severity at Diagnosis

Parameter	All (n = 2377)	Mild (n = 714)	Moderate (n = 1106)	Severe (n = 557)	P Value[a]
Progression of ARDS severity, No (%) [95% CI][b]					
Progression to moderate[c]		184 (25.8) [22.6-29.1]	N/A	N/A	
Progression to severe[c]		32 (4.5) [3.1-6.3]	140 (12.7) [10.8-14.8]	N/A	
Death in the 1st wk without category change		63 (8.8) [6.8-11.1]	126 (11.4) [9.6-13.4]	117 (21.0) [17.7-24.6]	
Invasive ventilation-free days to day 28, median (IQR), d[d]	10 (0-22)	16 (0-24)	11 (0-21)	0 (0-18)	<.001
Duration of invasive ventilation, median (IQR), d					
All patients	8 (4-15)	7 (3-14)	8 (4-16)	9 (4-16)	.04
Surviving patients	8 (4-15)	6 (3-13)	8 (4-15)	11 (6-18)	<.001
ICU length of stay, median (IQR), d					
All patients	10 (5-20)	10 (5-19)	11 (6-20)	11 (5-19)	.39
Surviving patients	11 (7-21)	10 (6-19)	12 (7-21)	14 (7-23)	.03
ICU mortality, No. (%) [95% CI]	838 (35.3) [33.3-37.2]	212 (29.7) [26.4-33.2]	387 (35.0) [32.2-37.9]	239 (42.9) [38.8-47.1]	<.001
Day 28 mortality, No. (%) [95% CI]	828 (34.8) [32.9-36.8]	211 (29.6) [26.2-33.0]	389 (35.2) [32.4-38.1]	228 (40.9) [36.8-45.1]	<.001
Hospital length of stay, median (IQR), d					
All patients	17 (8-33)	18 (10-33)	17 (8-33)	16 (6-31)	.22
Surviving patients	23 (14-40)	23 (14-40)	22 (13-40)	26 (14-43)	.41
Hospital mortality, No. (%) [(95% CI]	952 (40.0) [38.1-42.1]	249 (34.9) [31.4-38.5]	446 (40.3) [37.4-43.3]	257 (46.1) [41.9-50.4]	<.001

Abbreviations: ARDS, acute respiratory distress syndrome, ICU, intensive care unit; IQR, interquartile range.

[a] P value represents comparisons across the ARDS severity categories for each variable.

[b] Initial ARDS severity determined from worst partial pressure of oxygen to fraction of inspired oxygen ratio within first 24 hours following ARDS diagnosis.

[c] Most severe is calculated for time period up to day 7 postdiagnosis of ARDS. Analysis was limited to the first 7 days due to the less frequent sampling after that day.

[d] In patients in whom death occurs while receiving invasive mechanical ventilation, invasive ventilation-free days are counted as 0.

cardiac failure were associated with reduced likelihood of clinician recognition of ARDS (Table 2). The mean tidal volume was 7.5 mL/kg (95% CI, 7.4-7.6 mL/kg) of predicted body weight (PBW) among patients whose physicians recognized ARDS, marginally lower than that of 7.7 mL/kg (95% CI, 7.6-7.9 mL/kg) in patients whose ARDS was not recognized (P = .01). The mean PEEP level was 8.9 cm H_2O (95% CI, 8.8-9.1 cm H_2O) in patients whose ARDS was recognized, higher than that of 7.5 cm H_2O (95% CI, 7.3-7.7 cm H_2O) in patients whose ARDS was not recognized (P < .001). Physicians who recognized ARDS used adjunctive treatments more than physicians who did not (43.9% vs 21.7%, P < .001; eTable 4 in the Supplement). After adjusting for potentially confounding variables, there was no statistically significant association between clinician-recognized ARDS and tidal volumes (eTable 6 in the Supplement) or P_{plat} recording (eTable 7 in the Supplement). In contrast, clinician recognition of ARDS was statistically associated with the use of higher levels of PEEP, and greater use of prone positioning and neuromuscular blockade (eTables 8-10 in the Supplement).

ARDS Severity

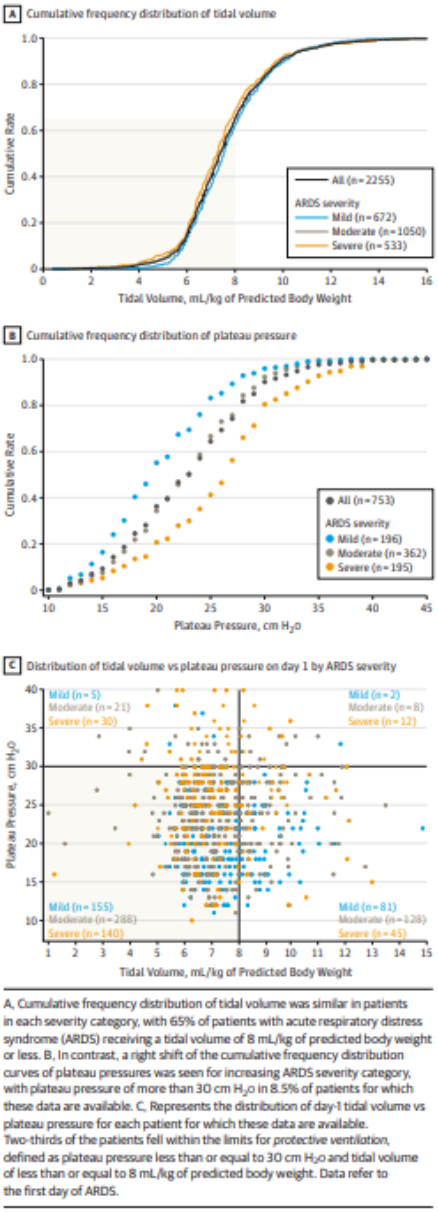
A total of 2377 patients developed ARDS in the first 48 hours of acute hypoxemic respiratory failure and received invasive mechanical ventilation. The period prevalence of mild ARDS was 30.0% (95% CI, 28.2%-31.9%); moderate, 46.6% (95% CI, 44.5%-48.6%); and severe, 23.4% (95% CI, 21.7%-25.2%) (Figure 1). Ventilator management differed among the ARDS severity groups, while the use of adjunctive measures increased and mortality was higher with greater ARDS severity (**Table 3**, **Table 4**, and **Table 5**). At diagnosis, increasing ARDS severity was paralleled by worsening Sequential Organ Failure Assessment (SOFA) scores, which was largely accounted for by the pulmonary component. The nonpulmonary component of the SOFA score was higher in patients with an increased ARDS severity category (Table 3). The $Paco_2$ increased and pH decreased in patients with increased ARDS severity category (Table 3, eFigure 1A-B in the Supplement). Three hundred sixteen patients (13.3%) with ARDS had a $Paco_2$ of 60 mm Hg or higher. However, the extent and severity of hypercapnia was relatively modest, even in severe ARDS.

Mechanical Ventilation in ARDS

Ventilator management varied with ARDS severity (Table 3). However, the decrease in tidal volume and increase in PEEP, from mild to moderate to severe ARDS, while statistically significant, was clinically modest (Table 3). In patients with ARDS 35.1% (95% CI, 33.1%-37.1%) received a tidal volume of more than 8 mL/kg PBW (**Figure 2**A and eFigure 1C in the Supplement), while 82.6% (95% CI, 81.0%-84.1%) received a PEEP of less than 12 cm H_2O.

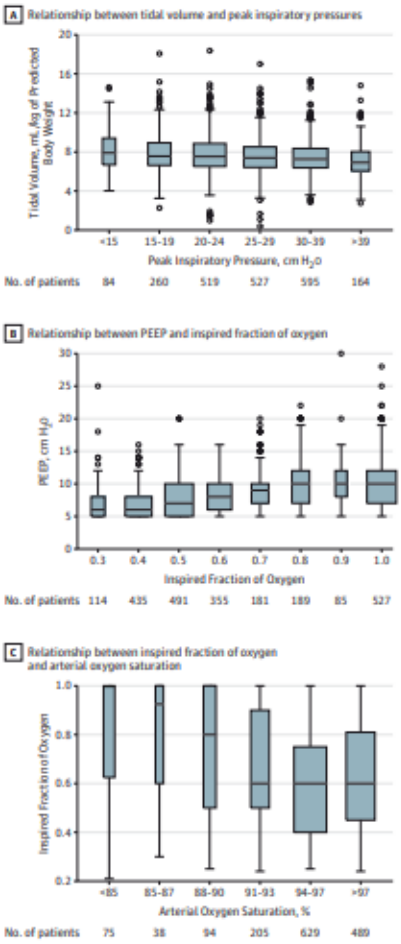
The distribution of P_{plat} differed significantly with ARDS severity (Figures 2B and eFigure 1D in the Supplement). P_{plat} was measured in 40.1% (95% CI, 46.0%-51.0%) of patients, irrespective of ARDS severity. This rose to 48.5% (95% CI, 46.0%-51.0%) of patients in whom there was no evidence for

Figure 2. Ventilation Parameters in Patients With ARDS



A, Cumulative frequency distribution of tidal volume was similar in patients in each severity category, with 65% of patients with acute respiratory distress syndrome (ARDS) receiving a tidal volume of 8 mL/kg of predicted body weight or less. B, In contrast, a right shift of the cumulative frequency distribution curves of plateau pressures was seen for increasing ARDS severity category, with plateau pressure of more than 30 cm H_2O in 8.5% of patients for which these data are available. C, Represents the distribution of day-1 tidal volume vs plateau pressure for each patient for which these data are available. Two-thirds of the patients fell within the limits for protective ventilation, defined as plateau pressure less than or equal to 30 cm H_2O and tidal volume of less than or equal to 8 mL/kg of predicted body weight. Data refer to the first day of ARDS.

Figure 3. Mechanical Ventilation Settings in Early Acute Respiratory Distress Syndrome



A, Tidal volume remained relatively constant across the range of peak inspiratory pressures. B, Positive end-expiratory pressure (PEEP) progressively increased in patients requiring higher inspired fraction of oxygen (F_{IO_2}). C, There was a stepwise increase in F_{IO_2} at lower arterial oxygen saturations, with F_{IO_2} steeply increasing at atrial oxygen saturation (S_{aO_2}) values lower than 91%. Data refer to the first day of ARDS.

For each box plot, the middle line represents the median, the lower hinge represents the first quartile, the upper hinge represents the third quartile, the whiskers extend to 1.5 times interquartile range, and the outliers are values outside the whiskers' range. The boxes are drawn with widths proportional to the square root of the number of observations in the groups. The numbers below each box plot represent the total number of patients in each group.

spontaneous ventilation. Two-thirds of patients in whom P_{plat} was reported received *protective mechanical ventilation* as defined by a tidal volume of 8 mL/kg of PBW or less and a P_{plat} of 30 cm H_2O or less (Figure 2C). In patients in whom P_{plat} was measured, 91.9% (95% CI, 88.1%-94.9%) of those receiving a tidal volume of more than 8 mL/kg PBW had a P_{plat} of 30 cm H_2O or less (Figure 2C). Less than 3% of patients received a tidal volume of more than 8 mL/kg and had a P_{plat} pressure of more than 30 cm H_2O (Figure 2C).

There was no relationship between tidal volume and either peak inspiratory pressure, P_{plat} or lung compliance (**Figure 3A** and eFigure 2 in the Supplement). Tidal volume was significantly higher in patients in a spontaneous breathing mode (7.5; 95% CI, 7.4-7.6 vs 7.9; 95% CI, 7.8-8.1 mL/kg PBW, $P < .001$; Table 3).

Positive end-expiratory pressure levels were relatively low (Table 3) and were higher in patients with higher peak inspiratory pressure and higher P_{plat}. In addition, no relationship was found between PEEP and the Pa_{O_2}/F_{IO_2} ratio, F_{IO_2} (Figure 3B) or lung compliance (eFigure 2 in the Supplement). In contrast, there was an inverse relationship between F_{IO_2} and Sp_{O_2}, suggesting that clinicians used F_{IO_2} to treat hypoxemia (Figure 3C).

Use of Adjunctive Measures

The use of adjunctive treatments in patients with ARDS on day 1 or 2 was relatively low but increased with ARDS severity (Table 4). Continuous neuromuscular blocking agents, high-dose steroids, and recruitment maneuvers were the most frequently used adjuncts. In patients with severe ARDS, continuous neuromuscular blockade was used in 37.8% (95% CI, 34.1%-41.2%), prone position in 16.3% (95% CI, 13.7%-19.2%), and recruitment maneuvers in 32.7% (95% CI, 29.3%-36.2%).

ARDS Outcomes

Severity of ARDS worsened in 356 (19.6%, 95% CI, 17.8%-21.5%) patients with mild or moderate ARDS (Table 5). There was a decreased likelihood of unassisted breathing (**Figure 4A**) and survival (Figure 4B) at day 28 with increasing severity. Overall, unadjusted ICU and hospital mortality from ARDS were 35.3% (95% CI, 33.3%-37.2%) and 40.0% (95% CI, 38.1%-42.1%), respectively (Figure 4 and Table 5). The number of ventilator-free days decreased (eFigure 3 in the Supplement), and the length of ICU–but not hospital–stay, increased with greater ARDS severity category. Both ICU and hospital survival decreased with increased ARDS severity (Table 5). Patients with a driving pressure (ie, P_{plat}-PEEP) of more than 14 cm H_2O on day 1 had a worse outcome (Figure 4C). There was a direct relationship between both plateau and driving pressure quintile and mortality rate (**Figure 5**).

Discussion

In this prospective study carried out in 459 ICUs in 50 countries in 5 continents, ARDS appeared to represent an impor-

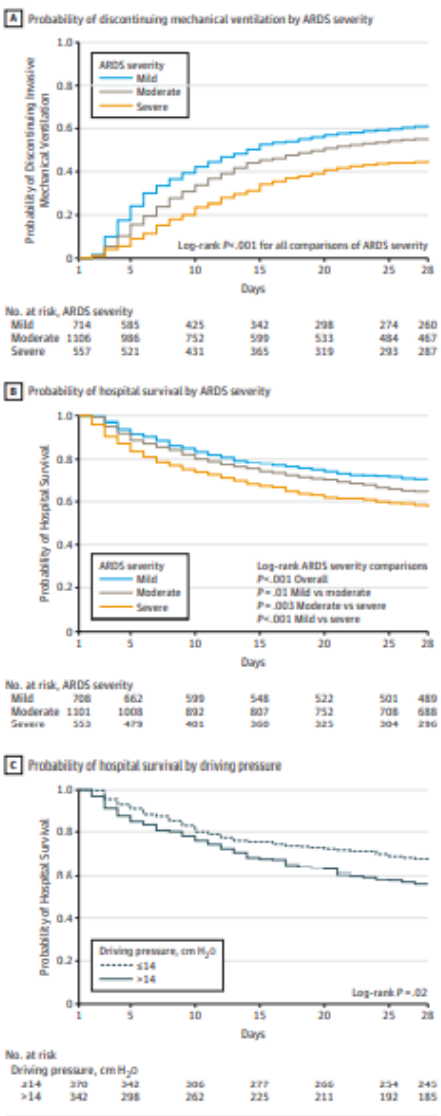
tant public health problem globally, with some geographic variation and with a very high mortality of approximately 40%. A major finding was the underrecognition of ARDS by clinicians, the low use of contemporary ventilatory strategies and adjuncts, and the limited effect of physician diagnosis of ARDS on treatment decisions. These findings indicate the potential for improvement in management of patients with ARDS.

In this study, the geographic variation in ARDS incidence ranged from 0.27 to 0.57 cases per ICU bed per 4 weeks and prcentage of ICU admissions. Because we could not estimate the population served by the ICUs in this study, we could not calculate population incidence for ARDS; therefore, relatively little can be inferred about the burden of ARDS in participating countries. The nearly 2-fold variation in ICU incidence in this study and the known variation in ICU resources internationally may well explain the variability in ARDS studies that involved specific geographic populations,[5] with the highest estimates in the United States[4,17] and Australia.[18,19] Our ICU incidence data are concordant with other estimates using similar approaches that have generated reliable population incidence data.[20]

These results suggest that ARDS continues to be underrecognized by clinicians in the era of the Berlin Definition, similar to previous findings using the American-European consensus conference (AECC) definition.[14,21-23] A key feature of our study design was that data were collected for each component of the Berlin Definition in all patients with hypoxemia breathing with the aid of a ventilator, which allowed us to identify patients with ARDS from the raw data. We chose this approach to enable a more robust evaluation of the incidence, as well to assess clinician recognition of ARDS. The rate of clinician recognition of ARDS was low, with 40% of all cases not being diagnosed. Clinician recognition rates increased with increasing disease severity but was still less than 80% in severe ARDS. Independent factors contributing to clinician recognition were younger patient age, lower predicted body weight, the presence of extrapulmonary sepsis or pancreatitis, and greater disease severity. Conversely, the absence of a risk factor for ARDS was associated with underrecognition of ARDS. Lower numbers of nurses and physicians per ICU patient were both associated with reduced clinician recognition of ARDS. It is possible that the way in which the data were collected contributed, in part, to clinician underrecognition of ARDS. Specifically, it is possible that the ICU clinician knew that the patient had ARDS, but this was not made known to the site investigators or reported in the patient chart. However, not indicating the diagnosis of ARDS in the chart constitutes a form of underrecognition. In addition, that the study had an explicit focus on ARDS, that all participants were offered online training on ARDS diagnosis, and that the case report form asked at 2 separate points in the study if the patient had ARDS, make this possibility less likely

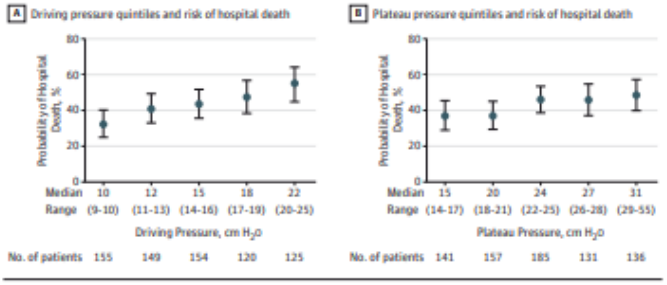
It is unclear whether clinician recognition of ARDS affects outcome because recognition may be only one of a number of barriers to the use of ventilatory and adjunctive

Figure 4. Outcome From Acute Respiratory Distress Syndrome



A, There was a lower likelihood of unassisted breathing with increasing severity of acute respiratory distress syndrome. B, There was a lower likelihood of survival to day 28 with increasing severity of acute respiratory distress syndrome (ARDS) at day 1. C, Patients with a driving pressure of greater than 14 cm H_2O on day 1 of ARDS criteria had a higher mortality.

Figure 5. Driving Pressure and Plateau Pressure and Outcome From ARDS



A, Mortality increased with increasing quintiles of driving pressure on first day of ARDS. B, The relationship between mortality and quintiles of plateau pressure is provided for comparison. Error bars indicate 95% confidence interval.

treatment strategies, while the sickest patients are more frequently diagnosed.[14,24] After adjusting for potential confounders, clinician diagnosis of ARDS was not independently associated with the use of lower tidal volume. Conversely, clinician diagnosis of ARDS was significantly associated with the use of higher PEEP, prone positioning, and neuromuscular blockade. Although the reasons for this are unclear, clinicians do not appear influenced by the presence or absence of ARDS for setting tidal volume and may be motivated by other factors (eg, perceived comfort, pH, $Paco_2$, etc).

Our data appear to demonstrate the predictive validity of the Berlin Definition, and are consistent with a recent observational study.[7] Increasing ARDS severity was associated with longer ICU stay, more days of invasive ventilation, longer hospital stays, and higher mortality. Patients with severe ARDS were younger, had fewer comorbidities but had a significantly worse outcome. The proportion of patients in each severity category was similar to that determined in retrospective analyses.[1]

ARDS appears to be undertreated in terms of the use of optimal, proven, or recommended approaches to mechanical ventilation and regarding the use of some adjunctive measures. Plateau pressure was reported in only 40.1% of all patients with ARDS, which increased to 48.5% of patients in whom there was no evidence for spontaneous ventilation. Although it is possible that patients in whom plateau pressure was measured were ventilated differently, this did not appear to be the case, at least in terms of tidal volume. We found no evidence to suggest that lower tidal volumes or higher PEEP were used in patients with a less compliant respiratory system or greater ARDS severity as reported in prior studies.[22] Low tidal volume ventilation was the most frequently used intervention, but more than one-third of all patients with ARDS received a tidal volume of more than 8 mL/kg of PBW, and approximately 60% received a tidal volume of more than 7 mL/kg of PBW. This finding is consistent with recent nonprotocolized RCTs in which patients received larger tidal volumes than expected.[4,5] In our study, PEEP was relatively low and constant across the spectrum of ARDS severity, with more than 80% of patients with ARDS receiving PEEP of 12 cm H_2O or less. Hypoxemia appeared to be treated predominantly by increasing Fio_2. High levels of permissive hypercapnia were infrequent. Adjunctive measures were used infrequently; this appeared to be the case for less expensive interventions such as prone positioning and neuromuscular blockade, as well as for expensive and invasive technologies such as extracorporeal membrane oxygenation. It is possible that the relatively low use of adjunctive measures such as neuromuscular blockade or prone positioning reflects ongoing uncertainty about the quality of evidence supporting these interventions.

ARDS continues to have a high mortality, despite advances in supportive care. There was a significant increase in mortality with each increase in ARDS severity category. Overall, 40% of patients with ARDS died in the hospital. Although detailed analyses of the factors contributing to outcome are beyond the scope of this article, we also confirmed a recent report[26] suggesting that higher driving pressure is associated with increased risk of death; albeit, our data should be interpreted cautiously as P_{plat} was available in a minority of patients.

This study has a number of limitations. Our focus on winter months, while allowing us to examine the burden of ARDS during the same season across the globe, may overstate ICU incidence figures for ARDS, due to specific diseases such as influenza.[27] In addition, despite enrolling a large number of ICUs from around the world, our convenience sample may be prone to selection biases that may limit generalizability; therefore, we are unable to calculate population-based incidence figures for ARDS. Similar to other epidemiological studies, we did not have access to the source data for the patients in the enrolling ICUs, so it is possible that not all patients with ARDS in participating centers were enrolled. However, enrollment of patients with ARDS from participating ICUs met expectations based on their recorded 2013 admission rates, while data from lower

recruiting ICUs was not different from that from higher enrolling ICUs, suggesting the absence of reporting biases. To ensure data quality, we instituted a robust data quality-control program in which all centers were requested to verify data that appeared inconsistent or erroneous. Although chest x-ray interpretation was performed by on-site clinicians, which potentially increased variability, we attempted to standardize interpretation by offering all the investigators web-based training. Another limitation is the lack of data collection concerning the use of conservative fluid strategy. Lastly, our assumption that patients discharged from the hospital before day 28 were alive at that time point is a further limitation.

Conclusions

Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized, undertreated, and associated with a high mortality rate. These findings indicate the potential for improvement in management of patients with ARDS.

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Author Contributions: Dr Pham and Dr Bellani had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bellani, Laffey, Pham, Fan, Brochard, Esteban, Gattinoni, Ranieri, Rubenfeld, Thompson, Wrigge, Slutsky, Pesenti.
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5.3 Anexo III: Trabalho original não integrado na investigação nuclear do ciclo de doutoramento, porém com ele relacionado, citado no capítulo de discussão, conclusões e trabalhos futuros

Outcomes of Acute Hypoxaemic Respiratory Failure. Insights from the Lung Safe Study

Tài Pham; Antonio Pesenti; Giacomo Bellani; Gordon Rubenfeld; Eddy Fan; Guillermo Bugedo; José Angel Lorente; **Antero do Vale Fernandes**; Frank Van Haren; Alejandro Bruhn Cruz; Fernando Rios; Jose A. Lorente; Andres Esteban, Luciano Gattinoni; Anders Larsson; Daniel F. McAuley; Marco Ranieri; B. Taylor Thompson; Hermann Wrigge; Arthur S. Slutsky; Laurent J. Brochard and John G. Laffey on behalf of the LUNG SAFE; Investigators and the European Society of Intensive Care Medicine Trials Group

Em revisão na revista *European Respiratory Journal*

ERJ-03317-2020, Fator de impacto: 12,242

Importância: Para além dos doentes com critérios de ARDS, a Insuficiência Respiratória Hipoxémica Aguda (IRHA) ainda é uma entidade não bem caracterizada.

Objetivos: Avaliar a incidência, as razões da hipoxémia, os outcomes dos doentes com IRHA e determinar se os doentes que não evoluíram com ARDS apresentam outcomes diferentes.

Projeto, cenário e participantes: Estudo de coorte prospetivo multicêntrico internacional (LUNG SAFE) de doentes que apresentam IRHA no início do curso de ventilação mecânica, conduzido durante 4 semanas consecutivas no inverno de 2014 em 459 UCIs de 50 países.

Exposições: IRHA definida por PaO_2 / FIO_2 de 300 mmHg ou menos, novos infiltrados pulmonares em imagiologia do tórax e necessidade de suporte ventilatório com pressão positiva no final da expiração (PEEP) de pelo menos 5 cm H2O.

Principais outcomes e medidas: O outcome primário foi a incidência de IRHA na UCI. Os outcomes secundários incluíram a distribuição das causas da hipoxemia, sobrevida hospitalar, fatores associados à mortalidade hospitalar e comparação de doentes com opacidades unilaterais versus bilaterais na imagem do tórax e preenchimento de outros critérios para ARDS.

Resultados: De 12.906 doentes em ventilação mecânica, 34,9% apresentaram critérios de IRHA com mortalidade hospitalar de 37,6%. A maioria dos doentes intubados com IRHA tinha critérios de ARDS (69,0%), enquanto 22,7% apresentavam opacidades unilaterais de imagem do tórax e 8,2% tinham insuficiência cardíaca congestiva (ICC) como principal causa de hipoxemia. Os doentes com ICC tiveram uma mortalidade de 44,1%, comparável ao ARDS (40,4%), embora os sobreviventes tenham tido menor tempo de ventilação mecânica e de permanência na UCI do que o ARDS. Doentes com IRHA unilateral apresentaram uma mortalidade não ajustada mais baixa, mas a mortalidade ajustada foi semelhante à do ARDS. A análise multivariada mostrou que o número de quadrantes envolvidos na imagem do tórax aumenta o risco de morte. A comparação de doentes com IRHA unilateral vs. ARDS com 2 quadrantes não mostrou diferença na mortalidade ajustada ou não ajustada.

Conclusões e relevância: A IRHA atinge 34,9% dos doentes em ventilação mecânica na UCI e a mortalidade hospitalar é de 37,6%. O outcome do doente depende mais do grau de envolvimento pulmonar do que do subtipo específico de IRHA presente, enfatizando a necessidade de enfocar o IRHA além do ARDS.

Outcomes of Acute Hypoxaemic Respiratory Failure. Insights from the Lung Safe Study

Tài Pham; Antonio Pesenti; Giacomo Bellani; Gordon Rubenfeld; Eddy Fan, Guillermo Bugedo; José Angel Lorente; **Antero do Vale Fernandes**; Frank Van Haren; Alejandro Bruhn; Fernando Rios; Andres Esteban, Luciano Gattinoni; Anders Larsson; Daniel F. McAuley; Marco Ranieri; B. Taylor Thompson; Hermann Wrigge; Laurent J. Brochard* and John G. Laffey* on behalf of the LUNG SAFE Investigators and the European Society of Intensive Care Medicine Trials Group
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Abstract

Background: The current incidence and outcome of Acute Hypoxaemic Respiratory Failure (AHRF) in the intensive care unit are unknown. Whether AHRF patients without acute respiratory distress syndrome (ARDS) have different outcomes than patients with ARDS has important implications.

Methods: An international, multicentre, prospective cohort study of patients presenting with AHRF early in the course of mechanical ventilation, conducted during 4 consecutive weeks in the winter of 2014 in 459 ICUs from 50 countries (LUNG SAFE). AHRF was defined by PaO_2/FiO_2 <300 mmHg, new pulmonary

infiltrates and mechanical ventilation with positive end-expiratory pressure (PEEP) of at least 5 cm H2O. ICU prevalence, causes of hypoxemia, hospital survival, factors associated with hospital mortality were measured. Patients with unilateral versus bilateral opacities were compared.

Findings: 12,906 critically ill patients received mechanical ventilation, and 34.9% had AHRF. Their hospital mortality was 38.6%. AHRF was related to ARDS (69.0%), to unilateral opacities (22.7%) or to congestive heart failure (8.2%, CHF). CHF patients had mortality comparable to ARDS (44.1%vs. 40.4%). Patients with unilateral-infiltrate had lower unadjusted mortality but similar adjusted mortality than ARDS. The number of quadrants on chest imaging was associated with an increased risk of death. There was no difference in mortality comparing patients with unilateral-infiltrate and ARDS with only two quadrants involved.

Interpretation

AHRF affects 34.9% of the patients receiving mechanical ventilation, and hospital mortality is 38.6%. Survival is dependent on the degree of pulmonary involvement, whether or not ARDS criteria are reached.

Funding: European Society of Intensive Care Medicine

246 words.

Trial registration

ClinicalTrials.gov Identifier: NCT02010073

Keywords: cardiac insufficiency; pneumonia; aspiration;

Take-Home Message

Patients with hypoxemic respiratory failure (AHRF) represent more than a third of patients requiring mechanical ventilation and their mortality often exceeds 40%. Mortality is similar for ARDS and unilateral AHRF when only two quadrants are involved on the chest X-Ray.

INTRODUCTION

Acute hypoxaemic respiratory failure (AHRF) is a leading cause of admission and need for mechanical ventilation in Intensive Care Units (ICU). Studies have usually focused on patients meeting the criteria for Acute Respiratory Distress Syndrome (ARDS) [1–3]. There are limited data on hypoxaemic patients who do not fulfil the definition of ARDS [4–6]. A large prospective observational study in Sweden, Denmark, and Iceland had examined patients with acute respiratory failure requiring mechanical ventilation regardless of the level of FiO_2 and found more than 20 years ago a mortality rate around 40% with or without ARDS [5].

AHRF patients without ARDS can have a cardiac failure or fluid overload, or only unilateral infiltrates on chest imaging. These patients are excluded from epidemiological studies addressing ARDS and exploring this population is important. First, the definition of ARDS is subject to variations into clinicians' interpretations such as the relative contribution of heart failure or fluid overload [7], and, or the analysis of chest X-ray for the diagnosis of bilateral pulmonary infiltrates [8-10]. Understanding the differential impact of unilateral versus bilateral airspace disease is also important because they may overlap with ARDS. In addition, it is essential to determine whether these patients can benefit from lung-protective approaches like those used for patients with ARDS [11, 12]. Although the underlying biological mechanisms may differ across these different groups, the symptomatic management of the lungs, e.g., ventilator settings, sedation, proning, could be comparable. Therefore, understanding the behaviour of hypoxaemic 'non-ARDS' ventilated patients might optimize the management strategy of these acutely hypoxaemic critically ill patients and may help to better understand the limits of the current ARDS definition.

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) is the most recent and largest international prospective cohort of patients with AHRF [1]. In this prespecified analysis, we set out to describe the global burden of AHRF and compare the different sub-groups of patients who make up AHRF: those who fulfil the criteria for the Berlin definition of ARDS; patients whose failure was entirely explained by cardiac failure or fluid overload as declared by clinicians; and patients with unilateral infiltrate on the chest imaging.

MATERIALS AND METHODS

Study Design

LUNG SAFE (ClinicalTrials.gov identifier NCT02010073) was a prospective multicentre observational study conducted in 459 ICUs from 50 different countries. All participating ICUs obtained ethics committee approval and patient consent or ethics committee waiver of consent, depending on local regulations. National coordinators and site investigators were responsible for obtaining ethics committee approval and for ensuring data integrity and validity. Participating centres screened all newly admitted patients for four consecutive winter weeks (February-March 2014 in the Northern hemisphere, June-August 2014 in the Southern hemisphere). A total of 4,499 patients had acute hypoxaemic respiratory failure (AHRF) defined by a PaO_2/FIO_2 <300 mmHg, new pulmonary infiltrates on chest imaging, and requirement of ventilator support with a positive end-expiratory pressure (PEEP) >5 cm H_2O. The detailed methods and design of LUNG SAFE have been previously described [1]; some results of this study have been reported in abstract form [13].

Participants and data definitions

Patients presenting with AHRF were divided into 3 groups:

- Acute Respiratory Distress Syndrome (ARDS): patients fulfilling the Berlin criteria for ARDS [4].
- Congestive Heart Failure (CHF): patients in whom respiratory failure was considered by clinicians to be fully explained by cardiac failure or fluid overload.
- Unilateral-infiltrate: patients fulfilling Berlin definition for ARDS criteria except that they presented with only unilateral infiltrates on chest imaging.

To ensure homogeneity in the analysis, we kept patients with early-onset (first 48 hours post ICU admission) of AHRF, not treated with ECMO in the first 48h, and not admitted to another ICU for >2 days before being transferred to the participating ICU.

Statistical analyses

Continuous variables are reported as mean ± SD or median (interquartile range [IQR]), and categorical variables as count and proportion. Comparisons of proportions were made using Chi-square and Fisher exact tests. Three groups were compared (unilateral-infiltrate, ARDS and CHF), and continuous variables were compared using ANOVA or Kruskall-Wallis test, as appropriate. We included geo-economic grouping in multivariable analyses, using the 2016 World Bank country classification [14]. When global comparisons were statistically significant, pairwise comparisons adjusting for multiple testing were performed using Tukey or Benjamini and Hochberg method.

Prognostic risk factors from previous literature and variables found to be associated in bivariate analysis with a P value <0.20 were entered in stepwise (forward and backward) multivariable logistic regression analyses with significance α levels of 0.05 or less for retention.

As basic analysis of chest imaging (quadrants involved) was an important focus, this component was introduced in mortality models using either: 1) considering bilateral opacities as a dichotomous variable; 2) considering the number of quadrants involved as an ordinal variable. To better examine the specific impact of bilateral versus unilateral opacities, mortality analyses were repeated restricting the population to patients having two quadrants involved whether they were unilateral (i.e. non-ARDS) or bilateral (i.e. ARDS).

Multicollinearity was evaluated with variance inflation factors for each variable and ruled out if the variance inflation factor was <4 (relatively conservative). The results are shown as odds ratios with 95% C. Models' performance was assessed using the Hosmer-Lemeshow goodness-of-fit test statistic. We used a Kaplan-Meier analysis to estimate the likelihood of hospital mortality or invasive ventilation discontinuation within 90 days of onset of AHRF.

No statistical power calculation was conducted before the study, and the sample size was based on available data. For all numerical variables, outliers were assessed and corrected by contacting site investigators if needed. The remaining outliers were plausible values that were kept in the analysis. No assumptions were made for missing data, and we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [15].

Statistical analyses were done with R (version 3.5.5, http://cran.r-project.org, accessed August 2019). All P values were two-sided, and values <0.05 were deemed statistically significant. Data are presented unadjusted unless specifically stated. We assumed that patients discharged alive from the hospital before 90 days were alive on day 90.

RESULTS

Prevalence and outcomes of AHRF in LUNG SAFE Cohort

A total of 29,144 patients were admitted to participating ICUs during the LUNG SAFE study, and 12,906 patients received mechanical ventilation. Among them, 4,499 patients (15.5% of the total admissions, and 34.9% of hypoxemic patients requiring mechanical ventilation) fulfilled criteria for AHRF with a mortality of 37.6% (1685/4481). The 4,499 AHRF patients represented 0.63 cases/ICU bed over four weeks.

N=3,834 (more than 85%) had data available in the two first days of AHRF (Figure 1). Patients receiving NIV or under early ECMO are shown in Figure 1, but they were not included in the subsequent analysis. The majority of patients (N=3,176; 83%) received invasive ventilation. Of the AHRF patients, 2193 (69.0%) fulfilled all the Berlin criteria for ARDS, 261 (8.2%) had CHF and 722 (22.7%) had unilateral-infiltrate, of whom 143 (19.8% of the latter group) developed full ARDS criteria (bilateral images) later during their ICU stay. The hospital mortality of patients with AHRF receiving invasive ventilation was 38.6%.

Patients with CHF

Patients with congestive heart failure were older, presented more frequent comorbidities such as diabetes, chronic renal failure or chronic cardiac failure (NYHA class 3 or 4), and less frequently chronic obstructive pulmonary disease (COPD) or immunocompromised status compared to patients with ARDS (Table 1 and e-Table 1). Many baseline characteristics were similar to patients with ARDS (SOFA score, arterial pH, PaO_2/FiO_2) but ventilatory parameters indicated lower PaCO2, PEEP and peak inspiratory pressure (PIP) (Tables 1 and 2). They

received higher tidal volumes, lower respiratory rates, and lower standardized minute ventilation (Table 2). Mortality was 44.1%, not different from the mortality of patients with ARDS (40.4%). Survivors from CHF had shorter durations of mechanical ventilation, length of stay in the ICU and in the hospital than ARDS (e-table 1).

Patients with unilateral-infiltrate

Characteristics

Compared to patients with ARDS, the 722 patients with unilateral-infiltrate had many similar characteristics. COPD was more frequent, but other comorbidities did not differ (Table 1 and e-Table 1). The three main risk factors for hypoxemia were similar in patients with unilateral-infiltrate and with ARDS, namely pneumonia, gastric aspiration and extrapulmonary sepsis. Aspiration was more frequent in patients in unilateral-infiltrate while pneumonia and extrapulmonary sepsis rates were more prevalent in ARDS.

Patients with unilateral-infiltrate had lower baseline respiratory and systemic illness severity than patients with ARDS, lower SOFA and non-pulmonary SOFA scores, and higher arterial pH, PaO_2/FiO_2 ratio, and lower PIP (Table 1). Plateau pressure (Plat) and driving pressure (reported in only 31.1% of the patients), were lower in patients with unilateral-infiltrate than in ARDS (Table 2, e-table 1 and Figure 2).

Management

Patients with unilateral-infiltrate received higher tidal volumes but lower PEEP, FiO_2, respiratory rate and standardized minute ventilation than patients with ARDS (Table 2).

'Protective' ventilation defined as receiving tidal volume lower than 8 mL/kg PBW and a plateau pressure lower than 30 cmH_2O (when available) was delivered at a similar rate in patients with unilateral-infiltrate and in patients with ARDS (63% vs 67%, P=0.250; e-Figure 1). The use of adjunctive therapies was low in the whole population but was higher in patients with ARDS than in unilateral-infiltrate patients (e-Table 2).

Unadjusted outcomes

Overall, unadjusted ICU and hospital mortalities were lower in patients with unilateral-infiltrate than in patients with ARDS (26% vs. 35% and 35% vs. 40%) (Table 2, e-Table 1 and Figure 3, panel A) and patients with unilateral-AHRF had more invasive-ventilation free days than patients with ARDS (Table 2). In an analysis confined to survivors, ICU stay was shorter in patients with unilateral-infiltrate than in patients with ARDS, but hospital length of stay was similar.

Impact of the number of quadrants involved in patients without CHF

1) Risk factors for death in unilateral-infiltrate and ARDS

Comparison of survivor's vs non-survivors is shown in e-Table 3. Multivariable analysis of the factors contributing to outcome in these patients with ARDS or unilateral-AHRF adjusting on main confounders demonstrated that the presence of bilateral opacities on the chest imaging (i.e. ARDS) was an independent risk factor for death (e-Table 4). A similar model adjusting on the same confounders using the number of quadrants involved instead of the bilateral opacities characteristics showed that having 3 or 4 involved quadrants was significantly associated with a higher risk of hospital mortality. Independent risk factors for mortality also included age, immunocompromised status, chronic liver failure, higher extrapulmonary SOFA score, concomitant cardiac failure, medical indication or trauma, and location in a middle-income country, higher respiratory rate and peak inspiratory pressure and lower ph. Conversely, higher body mass index, higher PEEP, drug overdose as the cause of respiratory failure were associated with better outcomes (e-Table 4). The multivariable analysis of factors associated with hospital mortality restricted to patients with unilateral-AHRF found similar results, although with less significant variables (e-table 5).

2) Patients with infiltrates in only two quadrants of chest X-ray

Of 1094 patients with two-quadrant infiltrates on CXR, 172 (16%) had unilateral opacities (unilateral-AHRF), while 922 (84%) had bilateral opacities (ARDS)

(Table 3). Unilateral-AHRF patients had more immunosuppression, gastric aspiration, contusions, and less extrapulmonary sepsis, but most of the other patients' characteristics, gas exchange variables and ventilator management were identical. The unadjusted mortality rates and different outcomes were similar between groups (Figure 3, panel B). In a multivariable analysis adjusting on the same covariates as the model performed for the whole population of AHRF, the presence of bilateral (vs. unilateral) opacities was not associated with mortality (e-Table 6).

3) Development of ARDS in patients presenting initially with unilateral-infiltrate

Of patients with unilateral-infiltrate on day 1 and 2, 143 (20%) subsequently developed ARDS. Patients who developed bilateral infiltrates were more severely ill than patients who never developed ARDS as evidenced by lower PaO2/FIO2 ratio in the first two days; higher hemodynamic SOFA score; lower pH; and higher PIP. Patients who developed ARDS had similar mortality rates but longer stays and duration of MV (e-Table 7). In multivariable analyses adjusting for age, SOFA score, pH and PF ratio, only PIP was associated with the evolution towards ARDS (e-Table 8).

DISCUSSION

The LUNG SAFE study shows that slightly more than a third of patients requiring mechanical ventilation in the participating ICU have PaO2/FIO2 ratio <300 mmHg. Patients with CHF receiving mechanical ventilation have a mortality rate comparable to patients with ARDS. Patients with unilateral-infiltrate have lower severity of illness than patients with ARDS, and the extent of the infiltrates on the chest imaging is associated with mortality. The outcome of patients with two-quadrant involvement on the chest X-ray is similar whether the distribution is bilateral (i.e. qualifying them for ARDS) or unilateral. In patients with unilateral AHRF, the peak pressure is the only independent risk factor for developing ARDS.

AHRF is prevalent among critically ill patients, representing more than 15% of all admissions and more than one-third of patients who received ventilation in this large international observational study. It has a high mortality rate. AHRF, as a whole, has an important impact on health-care systems worldwide, larger than ARDS alone [1, 16, 17]. While the subgroup with ARDS is well characterized and studied [1, 4], the population that have AHRF not fulfilling ARDS criteria is under-appreciated as a clinical entity and incidence and outcomes have not been often reported to date [5, 6, 18, 19]. The lack of consensual definition for AHRF and the heterogeneity of this group are potential explanations. In addition, ARDS is considered as an archetypal condition in the critically ill and has dominated the research agenda [20-24].

Few data are available for this category of patients. In a prospective study in Sweden, Denmark, and Iceland, Luhr et al. examined the prevalence and 90-d mortality of acute respiratory failure (ARF), defined as intubation and mechanical ventilation $\geqslant$ 24 h, as well as acute lung injury (ALI) and ARDS based on American-European consensus definition [5]. They did not use any oxygenation criteria for ARF, making comparisons difficult they included 1231 ARF patients, 287 ALI and 221 ARDS. Ninety-day mortality was 41% for all ARF, 42% for ALI and 41% for ARDS. The severity of illness and any chronic disease (except COPD) was more important for mortality and outcome than the definitions of ARDS if the patient was invasively ventilated more than 24 hours (defined as ARF). Vincent et al. reported the results of a sub study to validate the sequential organ failure assessment score looking at patients having PaO_2/FiO_2 below 200 mmHg and mechanical ventilation [6]. They reported a prevalence of 54% with an ICU mortality of 34%. In the present study, the SOFA is similar in ARDS and AHRF when the patients have more than two-quadrant opacities. The number of opacities seems to be a strong and noteworthy marker of severity of illness independent of whether it is defined as ARDS. This was an unexpected finding, given the low reproducibility of X-Ray imaging in intensive care [25]. The classification based on quadrants is, however, ultrasimple and may have a better reproducibility. In our study, patients presenting with ARDS and unilateral-AHRF had quite similar profiles. Comorbidities and main reasons for hypoxemia were comparable, although patients with aspiration were more frequent in unilateral injury. Patients with unilateral-infiltrate received slightly higher tidal volumes and

lower PEEP than patients with ARDS. When adjusted, similarly high mortality between patients with unilateral-infiltrate was observed compared to patients with ARDS and the same number of quadrants involved. This suggests that the extent of lung involvement is the predominant factor influencing the outcome, rather than the bilateral characteristic. There was a stepwise increase in mortality when the number of quadrants involved raised from 2 to 4, whereas patients with two quadrants, whether unilateral or bilateral, had the same outcomes.

Regarding the ARDS definition, our data confirm that patients with unilateral-infiltrate are not fundamentally different in terms of poor outcome from patients with ARDS [5]. They also have similar underlying risk factors, comorbidity profiles, are managed similarly. The need for subdividing these patients into ARDS and unilateral-infiltrate, at least based on the current clinical criteria, can be rediscussed depending on what is studied. Given the lack of knowledge regarding this condition, unilateral patients might be enrolled in studies of ARDS, perhaps with stratification based on the number of quadrants involved to understand if similar management approaches should be used. The pathophysiology or biological mechanisms differ, but the management may not be so different regarding, for instance, the ventilation of a baby lung. High PIP was the main risk factor for developing ARDS in patients with unilateral-infiltrate. The poor outcome of this population justifies further research.

Physiological studies looking at unilateral versus bilateral injury are needed to understand the impact of ventilator settings. For instance, the respective effects of PEEP or large tidal volumes in the presence of asymmetrical injury is an important question to address. Our data suggest that the same ventilator parameters seem to influence the outcome in unilateral or bilateral lung injury. The failure of current clinical criteria to meaningfully subgroup AHRF patients underlines the need to explore alternative classification approaches, including phenotyping based on biologic/immunologic profiles [26, 27] if specific treatments can be applied according to these phenotypes [28]. In our study, the basic clinical, though likely imperfect, classification of the number of quadrants involved had a strong prognostic value. Re-examining the impact of the number of quadrants may help to determine whether this parameter could be included as a severity criterion in the ARDS or AHRF definition.

Patients with cardiogenic AHRF receive a different therapeutic management approach compared to other types of AHRF. Although data are scarce, mechanical ventilation has always been associated with a poor prognosis [29, 30]. Although patients had a shorter duration of support, they had similar mortality than patients with ARDS, again in line with Luhr et al. [5]. One study compared outcomes of patients with cardiogenic pulmonary oedema to patients with ARDS [31]. In this retrospective study, authors found a four-fold increased risk of hospital mortality for patients with ARDS as compared to patients with cardiogenic pulmonary oedema, but definitions differed from ours (limited to need for mechanical ventilation and a PEEP of ≥5). This population of patients with cardiac failure may need more specific research attention. One could question the accuracy of the clinical classification of CHF by investigators in Lung SAFE. Differentiating ARDS from pure cardiac failure can be challenging [7, 32, 33] especially since the Berlin definition clearly states that patients could present with ARDS and concomitant heart failure [4] Patients were classified as CHF in the present study when hypoxemia was fully explained by cardiac failure or fluid overload per the treating clinician. This analysis reflects the clinical practice and the way patients are enrolled in or excluded from clinical trials.

Our study has the limitations of an observational design with the risk of unmeasured confounding factors. Regarding the quality of data collection, all numerical variables were checked, outliers were detected and queries to confirm their values were sent to investigators. This ensured the quality of our dataset and explains the low number of missing data, mostly reflecting lack of clinicians' monitoring of certain variables (e.g., plateau pressure).

CONCLUSION

Patients with AHRF represent a high global burden of illness, affecting one-third of the patients receiving ventilation in the ICU with mortality close to 40% in this cohort. Patients with unilateral-infiltrate have high mortality compared to patients with ARDS of similar severity. Regarding the outcome, the global extent of lung involvement seems more important than the unilateral vs. bilateral distribution of the lung opacities. These findings emphasize the need for greater attention to patients with unilateral-infiltrate in future studies.

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Table 1: Baseline and outcomes of all patients and separated by population category

	ARDS N= 2193	CHF N= 261	Unilateral-AHRF N= 722	Overall P value	N
Age, y	61.0±16.8	68.1±13.5*	62.1±17.2	<0.001	3176
Female gender, n(%)	821 (37.4%)	108 (41.4%)	254 (35.2%)	0.056	3012
Weight, kg	77.6±24.0	74.9±17.4	75.8±18.6	0.056	3012
BMI, kg/m2	27.3±8.6	26.9±5.8	26.5±6.2	0.061	2938
Illness Severity Indices					
SOFA Score	10.0 [7.0;13.0]	10.0 [8.0;12.0]	9.0 [6.0;12.0]*	<0.001	3161
Non-pulmonary SOFA score	6.7 [4.0;10.0]	7.0 [5.0;9.0]	6.0 [3.8;9.0]*	<0.001	3139
CXR quadrants involved				<0.001	2991
1	0 (0.0%)	34 (14.9%)	429 (71.4%)		
2	922 (42.6%)	72 (31.6%)	172 (28.6%)		
3	507 (23.5%)	33 (14.5%)	0 (0.0%)		
4	733 (33.9%)	89 (39.0%)	0 (0.0%)		
Bilateral opacities	2193 (100.0%)	187 (74.8%)*	0 (0.0%)	<0.001	3165
PaCO2, mmHg	45.9±14.9	42.8±14.3*	44.8±15.2*	0.003	3133
pH	7.32±0.12	7.33±0.13	7.34±0.12*	<0.001	3133
PaO2/FiO2, mmHg	161.0±67.9	170.8±67.4	190.0±63.8*	<0.001	3159
Worst PaO2/FiO2 in the first 2 days, mmHg	153.2±66.1	159.0±64.3	178.7±62.8*	<0.001	3170
Initial Severity, n(%)		*	*	<0.001	3169
Mild	663 (30.2%)	87 (34.3%)	330 (45.7%)		
Moderate	1024 (46.7%)	120 (47.2%)	313 (43.4%)		
Severe	506 (23.1%)	47 (18.5%)	79 (10.9%)		
Comorbidities, n(%)					
Diabetes	482 (22.0%)	79 (30.3%)*	158 (21.9%)	0.009	3176
COPD	448 (20.4%)	38 (14.6%)*	179 (24.8%)*	0.001	3176
Chronic Renal Failure	210 (9.6%)	51 (19.5%)*	68 (9.4%)	<0.001	3176
Immunosuppression	455 (20.7%)	16 (6.1%)*	133 (18.4%)	<0.001	3176
Chronic Cardiac Failure	211 (9.6%)	106 (40.6%)*	71 (9.8%)	<0.001	3176
Chronic Liver Failure	96 (4.4%)	5 (1.9%)	28 (3.9%)	0.157	3176
At least 1 comorbidity	1287 (58.7%)	181 (69.3%)*	425 (58.9%)	0.004	3176
"Cause of hypoxaemia" (more than 1 cause is possible), n(%)					
Pneumonia	1478 (67.4%)	17 (6.5%)*	453 (62.7%)*	<0.001	3176
Non pulmonary Sepsis	384 (17.5%)	11 (4.2%)*	103 (14.3%)*	<0.001	3176
Gastric aspiration	357 (16.3%)	22 (8.4%)*	149 (20.6%)*	<0.001	3176
Trauma	103 (4.7%)	3 (1.1%)*	47 (6.5%)	0.002	3176
Pancreatitis	47 (2.1%)	0 (0.0%)*	10 (1.4%)	0.013	3176
Pulmonary contusion	74 (3.4%)	3 (1.1%)	34 (4.7%)	0.023	3176
Pulmonary Vasculitis	29 (1.3%)	1 (0.4%)	6 (0.8%)	0.356	3176

Non cardiogenic Shock	184 (8.4%)	6 (2.3%)*	46 (6.4%)	0.001	3176
Overdose	45 (2.1%)	0 (0.0%)*	21 (2.9%)	0.018	3176
TRALI	98 (4.5%)	11 (4.2%)	24 (3.3%)	0.412	3176
CHF	326 (14.9%)	261 (100.0%)*	75 (10.4%)*	<0.001	3176
COPD	218 (9.9%)	0 (0.0%)*	103 (14.3%)*	<0.001	3176
Asthma	30 (1.4%)	0 (0.0%)	11 (1.5%)	0.101	3176
No Cause identified	94 (4.3%)	0 (0.0%)*	34 (4.7%)	0.002	3176

*:P<0.005 vs ARDS

Table 2: Ventilatory Management and Outcomes in Patients with AHRF and with ARDS

	ARDS patients N=2193	CHF N=261	Unilateral-AHRF N=722	P value	N
Ventilation Management					
VT, ml/kg PBW	7.7±1.8	8.3±1.8*	7.9±1.9*	<0.001	3009
RR, b/min	20.8±8.7	18.9±5.6*	19.1±5.5*	<0.001	3155
PEEP, cmH2O	8.0 [5.0;10.0]	6.0 [5.0;8.0]*	6.0 [5.0;8.0]*	<0.001	3159
FiO2	0.6 [0.4;0.8]	0.6 [0.4;0.9]	0.5 [0.4;0.6]*	<0.001	3161
Plateau pressure, cmH2O	23.3±6.1	21.8±5.8	20.1±5.2*	<0.001	1002
Driving pressure, cmH2O	14.9±5.6	14.0±5.4	13.1±4.9*	<0.001	999
PIP, cmH2O	26.9±8.2	24.7±8.2*	24.8±8.0*	<0.001	3041
Minute ventilation (standardized), L/min	10.87±4.77	9.95±4.49*	10.20±4.41*	<0.001	3103
Outcomes					
Duration of invasive MV - in hospital survivors, days	8.0 [4;15] 8.0 [4;14]	4 [2;9]* 4.0 [3;10]*	6 [3;12]* 6 [3;12]*	<0.001 <0.001	3003 1784
VFD, days	11.0 [0;20]	16 [0;24]	18 [0;24]*	<0.001	3003
ICU Length of Stay - in ICU survivors, d	10 [5;19] 11 [6;20]	6 [3;12]* 7 [4;13] *	9 [5;16]* 9 [5;17]*	<0.001 <0.001	3176 2116
Hospital Length of Stay - in hospital survivors, days	17 [8;32] 23 [13;40]	12 [5;24]* 19 [11;31] *	17 [9;30]* 21 [13;36]*	<0.001 0.008	3108 1882
ICU mortality, n(%)	774 (35.3%)	98 (37.5%)*	188 (26.0%)*	<0.001	3176
Hospital mortality, n (%)	882 (40.4%)	115 (44.1%)*	229 (31.8%)*	<0.001	3165

PBW: predicted body weight

Table 3: Demographics, illness severity, management and outcomes of patients with AHRF and with ARDS with 2 CXR quadrants involved

	Unilateral-AHRF with 2 quadrants N=172	**Bilateral with 2 quadrants(ARDS) N=922**	**p-value**	**N**
Age, y	61.2±18.0	62.3±16.6	0.452	1094
Female gender, n(%)	63 (36.6%)	356 (38.6%)	0.685	1094
Weight, kg	75.1±20.8	78.2±26.8	0.104	1032
BMI, kg/m2	25.9±6.5	27.6±10.2	0.008	1008
SOFA	9.6 [7.0;12.0]	9.8 [7.0;12.0]	0.249	1094
Comorbidities, n(%)				
Diabetes	40 (23.3%)	210 (22.8%)	0.969	1094
COPD	36 (20.9%)	201 (21.8%)	0.878	1094
Chronic Renal Failure	15 (8.7%)	96 (10.4%)	0.591	1094
Immunosuppression	43 (25.0%)	157 (17.0%)	0.018	1094
Chronic Cardiac Failure	16 (9.3%)	91 (9.9%)	0.928	1094
Chronic Liver Failure	4 (2.3%)	34 (3.7%)	0.504	1094
At least 1 comorbidity	103 (59.9%)	536 (58.1%)	0.732	1094
"Cause of hypoxaaemia" (more than 1 cause is possible), n(%)				
Pneumonia	118 (68.6%)	584 (63.3%)	0.217	1094
Non pulmonary Sepsis	21 (12.2%)	177 (19.2%)	0.038	1094
Gastric aspiration	43 (25.0%)	147 (15.9%)	0.006	1094
Trauma	13 (7.6%)	57 (6.2%)	0.612	1094
Pancreatitis	0 (0.0%)	22 (2.4%)	0.036	1094
Pulmonary contusion	16 (9.3%)	40 (4.3%)	0.012	1094
Oxygenation and Ventilation				
PaO2/FiO2, mmHg	185±63	178±66	0.196	1094
Mild	56 (32.6%)	318 (34.5%)	0.509	1094
Moderate	91 (52.9%)	446 (48.4%)		
Severe	25 (14.5%)	158 (17.1%)		
PaCO2, mmHg	46±15	44±13	0.134	1084
pH	7.33±0.12	7.34±0.11	0.148	1084
FiO2	0.5 [0.4;0.8]	0.5 [0.4;0.7]	0.247	1094
Vt, ml/kg PBW	7.6±1.8	7.8±1.7	0.153	1046
RR, b/min	20±6	20±6	0.444	1091
Minute ventilation, L/min	10.33±4.50	10.31±4.62	0.942	1071
PEEP, cmH20	6.0 [5.0;10.0]	8.0 [5.0;10.0]	0.101	1094
Plateau pressure (n=336), cmH20	20.8±5.8	21.8±5.4	0.238	336
Driving pressure (n=336), cmH20	13.1±5.9	14.1±4.9	0.282	336
PIP (n= 1056), cmH20	25.9±8.2	25.7±8.0	0.847	1056
Outcomes				
Duration of invasive MV - in hospital survivors, dyas	7 [3;12] 7 [4;13]	7 [4;14] 7 [4;14]	0.281 0.844	1036 652
VFD28, days	16 [0;23]	15 [0;23]	0.581	1036

ICU LOS - in ICU survivors, days	9 [5;16] 10 [6;16]	10 [5;19] 11 [6;20]	0.291 0.402	1094 766
Hospital LOS - in hospital survivors, days	17 [10;35]	17 [9;33]	0.866	1070
ICU mortality, n(%)	48 (27.9%)	280 (30.4%)	0.578	1094
Hospital mortality, n(%)	58 (33.9%)	328 (35.7%)	0.720	1090

PBW: predicted body weight

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Figure legends

Figure 1: Flowchart of the patients screened and included in the analysis
Abbreviations: AHRF: Acute Hypoxaemic Respiratory Failure; ARDS: Acute Respiratory Distress Syndrome; CHF: Congestive Heart Failure; ECMO: ExtraCorporeal Membrane Oxygenation; NIV: Non-invasive Ventilation

Figure 2: Boxplots of respiratory parameters according to the population category (Unilateral-infiltrate in blue vs ARDS in black). P-values are results of Student test comparisons. Outliers appear as dots.
Panel A: Tidal Volume the first day of AHRF. Data is available for 2769 patients (95.0% of the patients).
Panel B: Plateau pressure on the first day of AHRF. Data is available for 912 patients (31.2% of the patients).
Panel C: Driving pressure on the first day of AHRF. Data is available for 910 patients (31.2% of the patients).
Abbreviations: AHRF: Acute Hypoxemic Respiratory Failure; ARDS: Acute Respiratory Distress Syndrome; mL/kg PBW: millilitre per kilogram of predicted body weight; Pplat: plateau pressure

Figure 3A: Probability of discontinuing mechanical ventilation and of hospital survival in patients with unilateral-infiltrate (Blue) vs ARDS (Black). Solid lines represent the probability of hospital survival and dotted lines, the probability of mechanical ventilation discontinuation. P-values are the results of log-rank tests.

Figure 3B: Probability of discontinuing mechanical ventilation and of hospital survival in patients with two quadrants and unilateral-infiltrate (Blue) vs 2 quadrants and ARDS (Black). Solid lines represent the probability of hospital survival and dotted lines, the probability of mechanical ventilation

Figure 1: Flow of patients

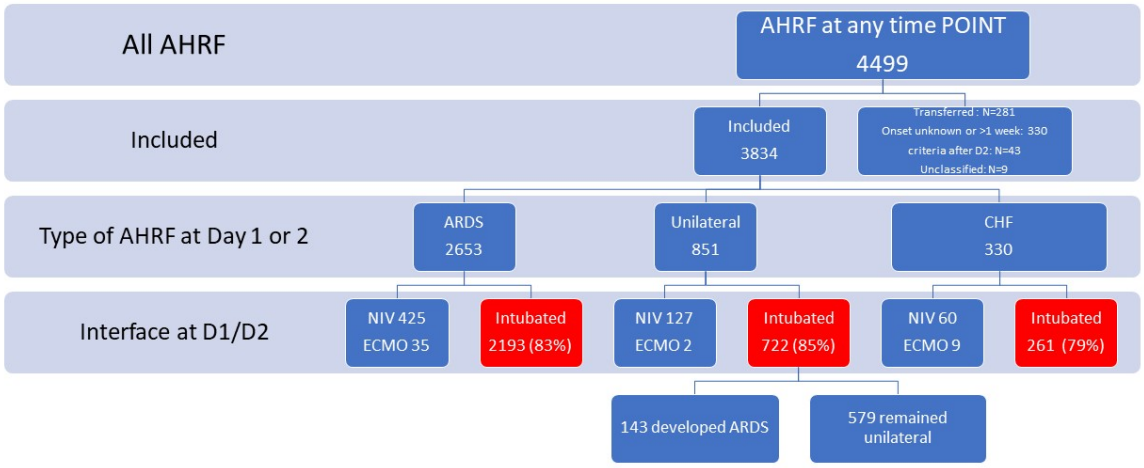


Figure 2: Mechanical ventilation parameters in patients with unilateral-AHRF or ARDS

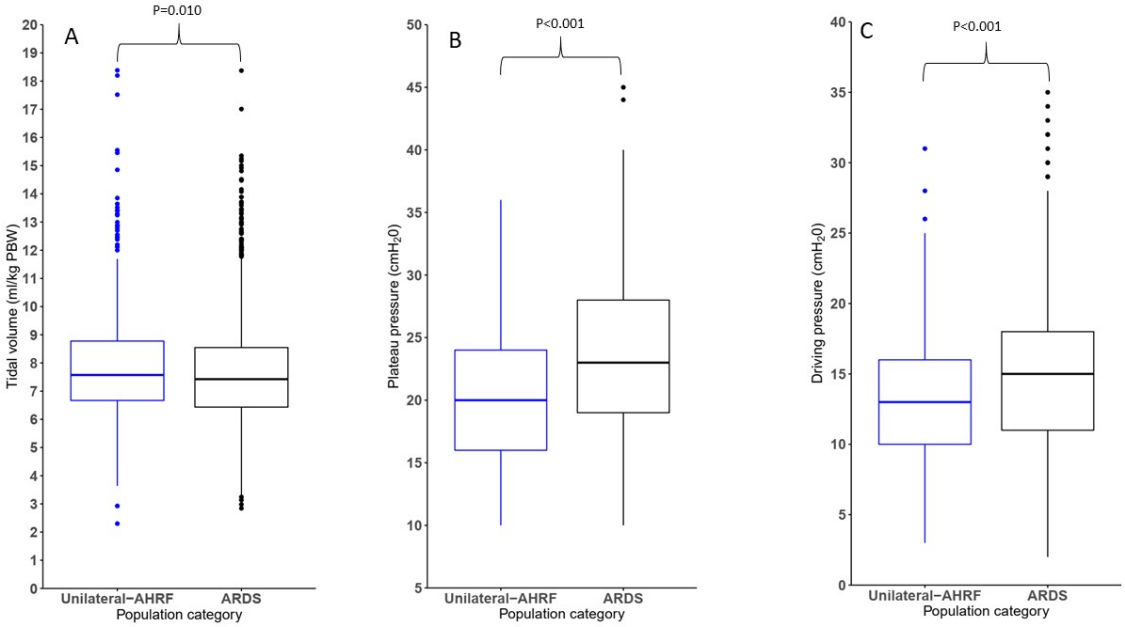


Figure 3 Panel A: Probability of discontinuing mechanical ventilation and of hospital survival in patients with unilateral-AHRF vs ARDS

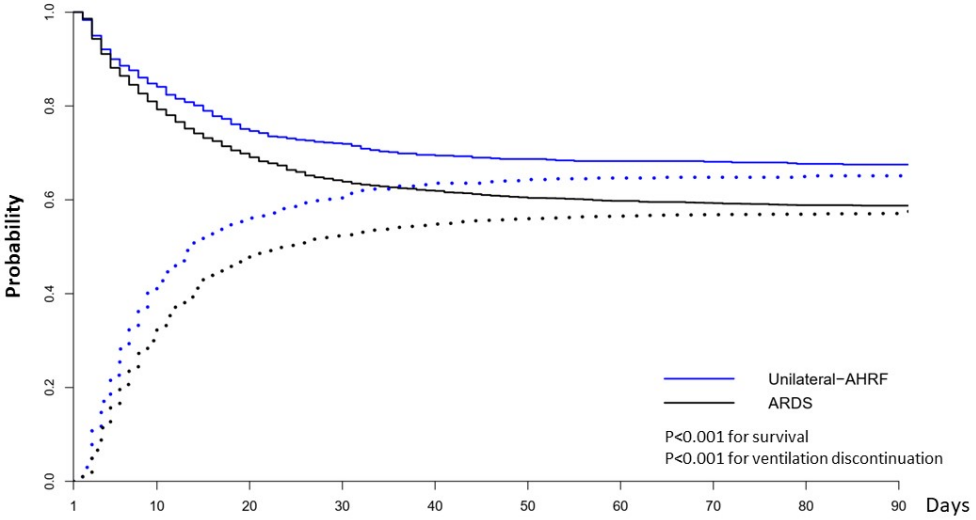
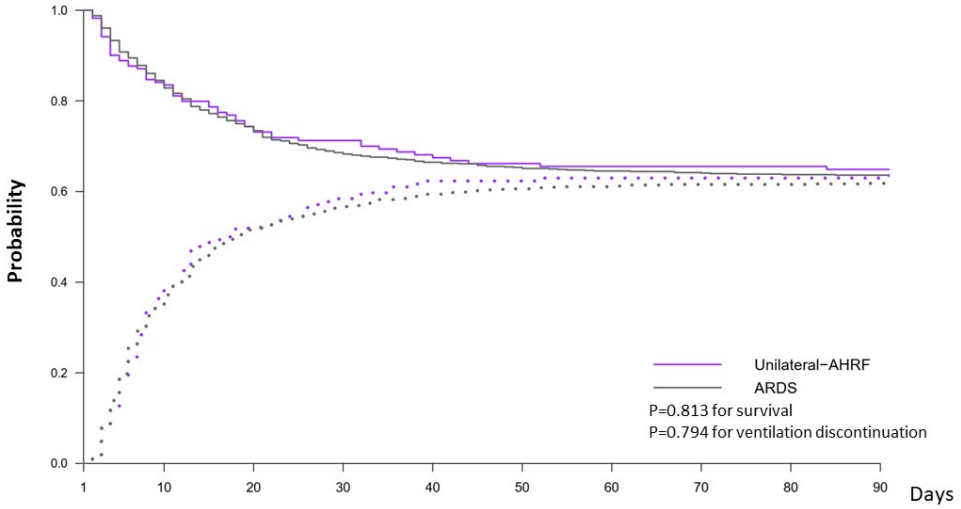


Figure 3 Panel B: Probability of discontinuing mechanical ventilation and of hospital survival in patients with 2 quadrants involved and unilateral AHRF vs ARDS



5.4 Anexo IV: Outros trabalhos científicos efetuados na forma de capítulos publicados em livro, comunicações orais e posters, e palestras realizadas, em relação com a investigação base do ciclo de doutoramento

Capítulos publicados em livro

1. **Antero Fernandes**, Paula Mendes, Lúcio Lara Santos. ***Insuficiência Respiratória Perioperatória***. Secção V: Respiratório: Tratado Lusófono de Medicina Intensiva. Editores: Fernando Suparregui Dias, Rui Moreno, Ederlon Rezende, Ciro Leite Mendes, Antero Fernandes. AMIB, SPCI. Editora Atheneu. Rio de Janeiro, Brasil. Em publicação.

Trabalhos apresentados na forma de comunicação oral e póster

1. Pedro Correia de Azevedo, Rui Gomes, Lucinda Oliveira, **Antero Fernandes**. ***Pneumonia associada ao ventilador***. XVIII Congresso Nacional de Medicina Intensiva. 12 de maio de 2015. Lisboa, Portugal.
2. Rita Varudo, Inês Pimenta, Vânia Brito, **Antero Fernandes**. ***Pneumonia como complicação pós-operatória numa unidade de cuidados intensivos***: ***preditores de mortalidade e influência dos isolamentos bacterianos nos outcomes***. XXI Congresso nacional de Medicina Intensiva. 10 - 12 de maio de 2018, Porto.
3. Rita Varudo, Inês Pimenta, Vânia Brito, **Antero Fernandes**. ***Pneumonia pneumocócica numa numa unidade de cuidados intensivos: aplicação do score SCAP na identificação precoce de doença grave***. XXI Congresso nacional de Medicina Intensiva. 10 - 12 de maio de 2018, Porto.
4. **Antero Fernandes**, Rafael Costa, L. Lara Santos. Iposcore – ***Prever o risco de complicações do tratamento cirúrgico e definir o prognóstico em pacientes com cancro através da integração de dados patológicos e clínicos***. Fundação para Ciência e Tecnologia. Lisboa, outubro de 2018.

5. R. Castro, **A. Fernandes**, C. Salomé, L. Antunes, R. Costa, J. Abreu Sousa, L. Lara Santos. ***Identify patients at risk for surgery who benefit from a pre-habilitation program: Preliminary results***. In abstract book of the 13 th International Gastric Cancer Congress. 8 - 11 May 2019, Prague, Czech Republic.

Palestras efetuadas

1. **Antero Fernandes**. Palestrante: ***Insufciência Respiratória pós-operatória***. Instituto Português de Oncologia, Porto. março de 2017.
2. **Antero Fernandes**. Palestrante: XV Congresso nacional de cancro digestivo. ***Cancro da Junção esófago-gástrica. Papel da Medicina Intensiva***. Curso pré-congresso, Albufeira, 10-12 de maio, 2019.
3. **Antero Fernandes**. Palestrante: ***Volume corrente de 6 ml /kg PBW para todos os doentes ventilados? Particularizando os doentes cirúrgicos com complicações pulmonares***. VI Congresso internacional de cuidados intensivos. XVI congresso do Arco Ibero-Atlântico. 1-2 de abril de 2019. Porto, Portugal.
4. **Antero Fernandes**. Palestrante: ***Pro - contra: Volume corrente de 6 ml /kg para todos os doentes ventilados? Particularizando os doentes cirúrgicos com complicações pulmonares.*** XXII Congresso Nacional Medicina Intensiva. VIII congresso Luso-brasileiro de Medicina Intensiva. Lisboa, Portugal, 2-4 de maio de 2019.
5. **Antero Fernandes**. Palestrante: ***Complicações pulmonares pós-operatórias. Abordagem em cuidados intensivos***. VI Congresso internacional de cuidados intensivos. XVI congresso do Arco Ibero-Atlântico. 1-2 de abril de 2019. Porto.
6. **Antero Fernandes**. Palestrante: ***Ainda existe lugar para manobras de recrutamento alveolar no ARDS em 2021? Particularizando os doentes cirúrgicos com complicações pulmonares***. VI Congresso internacional de cuidados intensivos. XVI congresso do Arco Ibero-Atlântico. 1-2 de abril de 2019. Porto.

7. **Antero Fernandes**. Palestrante: ***Proning - Quando começar? Particularizando os doentes cirúrgicos com complicações pulmonares***. VI Congresso internacional de cuidados intensivos. XVI congresso do Arco Ibero-Atlântico. 1-2 abril de 2019. Porto.
8. **Antero Fernandes**. Palestrante: ***Pro-Contra Corticoides na sepsis: Particularizando a sepsis pós-operatória. Os resultados do Adrenal Study mudam a nossa conduta?*** VII congresso Luso-Brasileiro de Medicna Intensiva-17-19 de maio de 2018. Salvador da Baia, Brasil.
9. **Antero Fernandes**. Palestrante: ***Sépsis pós-operatória. Os Novos métodos de ventilação mecânica são verdadeiramente utéis?*** VII congresso Luso-Brasileiro de Medicina Intensiva-17-19 de maio de 2018. Salvador da Baia, Brasil.
10. **Antero Fernandes**. Palestrante. ***Como Eu faço a abordagem do choque refratário nos doentes cirúrgicos***. VII congresso Luso-Brasileiro de Medicina Intensiva-17-19 de maio de 2018.Salvador da Baia, Brasil.

5.5 Anexo V: Abstract: Identify patients at risk for surgery who benefit from a pre-habilitation program: Preliminary results

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Objectives

The aim of this study is to create and validate a new score to predict the risk of postoperative complications in esophagogastric surgery.

Methods

This is an observational retrospective study. Based on the preexisting scores like P-Possum, ACS and ARISCAT, a new score was developed (MyIPOrisk-score). Using the Clavien-Dindo classification for postoperative complications (major vs minor/none) as the outcome and the three referred scores as explanatory variables; a logistic regression model was fitted to a sample of 496 patients. This new score was applied to a set of 58 risk patients submitted to esophagogastric surgery between July 2016 and April 2018 and admitted on the post-operative period in an intensive or intermediate care unit.

Results

Fourteen patients had significant postoperative complications. The sensitivity and specificity of IPO score were 85.7% and 65.1%, respectively, compared to Charlson Index with 71.4% and 18.6%, P-Possum with 50% and 81.4%, ACS with 71.4% and 44.2% and ARISCAT with 100% and 11.6%.

Conclusions

Those are preliminary results of more considerable work, in progress. It was shown that in this population IPO score was a better predictor for morbidity and

mortality than other scores. We intend to extend the study to a larger sample with the same characteristics to validate the score and establish it as an indicator for pre-habilitation need.

5.6 Anexo VI: Capítulo de Insuficiência Respiratória Perioperatória: Tratado Lusófono de terapia Intensiva. Em Publicação-Editora Atheneu. Rio de Janeiro, Brasil.

Seção V – Sistema Respiratório

Capítulo 56.8 - Insuficiência Respiratória Perioperatória

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INSUFICÊNCIA RESPIRATÓRIA PERIOPERATÓRIA

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    3.2 Tipo 2 (Hipercápnica / Ventilatória)
    3.3 Tipo 3 (Perioperatória)
    3.4 Tipo 4 (Choque)
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    4.1 Causas multifatoriais
5. Sinais Clínicos e Sintomas
6. Avaliação diagnóstica da etiologia da hipoxemia e da hipercapnia
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DESTAQUES

- O sistema respiratório é particularmente vulnerável aos efeitos da anestesia geral e da cirurgia, e no período pós-operatório o compromisso respiratório é comum.

- Em geral, os efeitos residuais da anestesia, a dor pós-operatória e a alteração da mecânica toraco-abdominal contribuem para diminuir a capacidade residual funcional (CRF), originando um colapso progressivo das unidades alveolares dependentes.

- A Insuficiência respiratória aguda é comum no período pós-operatório, sendo a atelectasia a sua causa mais frequente.

- A insuficiência respiratória perioperatória, também designada insuficiência respiratória aguda (Tipo 3) representa geralmente um subconjunto da insuficiência respiratória do tipo 1, porém às vezes é considerada separadamente porque é muito comum.

- A síndrome clinica reflete os sinais e sintomas de hipoxemia, hipercapnia ou do aumento do trabalho respiratório compensatório.

- O diagnóstico de insuficiência respiratória perioperatória é essencialmente clínico, devendo sempre ser confirmado laboratorialmente, através da gasometria arterial.

- A imagiologia do tórax e muito importante para o diagnóstico, no qual a avaliação do raio - X do tórax se revela de grande importância, sobretudo em termos etiológicos, e a ultrassonografia pode dar-nos um diagnóstico preciso das condições que comumente causam insuficiência respiratória aguda, podendo melhorar a precisão geral do diagnóstico, particularmente em ambiente de cuidados intensivos, comparativamente as abordagens de diagnóstico padrão.

- O manejo da insuficiência respiratória aguda pode ser dividido em uma fase de ressuscitação urgente seguida de uma fase de atendimento contínuo e quase todos os doentes necessitam de oxigénio suplementar.

- Apesar de dados limitados e da necessidade de novos ensaios randomizados, a ventilação não invasiva sob pressão positiva (VPPNI) pode ser considerada uma ferramenta profilática e terapêutica na melhoria das trocas gasosas no período pós-operatório.

- A potencial gravidade da insuficiência respiratória pós-operatória poderá necessitar de recurso a ventilação mecânica invasiva por pressão positiva (VIPP), onde diferentes estratégias de abordagem poderão ser tidas em conta, em dependência da etiologia presente.

1. INTRODUÇÃO

O sistema respiratório é particularmente vulnerável aos efeitos da anestesia geral e da cirurgia, e o compromisso do sistema respiratório no período pós-operatório é comum, sendo que as suas alterações podem ocorrer ainda na indução da anestesia geral, podendo o sistema respiratório levar até 6 semanas para retornar ao estado pré-operatório em cirurgias de grande magnitude. [1,2,3]

O drive respiratório, função muscular e os volumes pulmonares alteram-se de forma frequente, e a atelectasia, enquanto principal causa de insuficiência respiratória aguda perioperatória (IRAPO) desenvolve-se em mais de 75% dos doentes que recebem um medicamento bloqueador neuromuscular. [1,2,3]

Em doentes jovens e saudáveis, as alterações do sistema respiratório são geralmente moderadas e bem toleradas, mas em idosos e em doentes com doença pulmonar pré-existente pode ter sérias consequências. [4]

Vários fatores de risco para o desenvolvimento de complicações no período pós-operatório (CPOs) e em particular as complicações pulmonares pós-operatórias (CPPO) causadoras de IRAPO estão descritos na literatura, e os médicos devem estar cientes dos fatores não modificáveis e modificáveis, reconhecendo a sua importância, no intuito de intervir precocemente através da otimização dos cuidados perioperatórios, de forma a mitigar o risco de desenvolvimento de CPOs.

A ocorrência de anormalidades, doenças ou disfunções clinicamente significativas, relacionadas ao sistema respiratório, e que alterem negativamente o curso clínico do doente após um procedimento cirúrgico, define o conceito de complicação pulmonar pós-operatória (CPPO). Integram este grupo: atelectasias clinicamente relevantes, broncospasmo, traqueobronquites, pneumonias, síndrome de distress respiratório agudo (SDRA), insuficiência respiratória, necessidade de ventilação mecânica invasiva ou não invasiva prolongada (> 48 horas) e exacerbações de doenças pulmonares pré-existentes. [5,6]

A magnitude das complicações pós-operatórias (CPO) causadoras de IRAPO é sobejamente reconhecida, porquanto para além do elevado custo económico estão associadas ao aumento da mortalidade, sendo muito importante a avaliação pré-operatória e os adequados cuidados perioperatórios.

Muitos modelos de previsão de risco perioperatório estão descritos e validados, revelando-se de grande utilidade na melhoria da nossa compreensão de desenvolvimento de CPPO, continuando, contudo, a haver um consenso inadequado sobre o grau de sensibilidade e especificidade dos diferentes scores preditivos de risco em prever CPO e até a própria mortalidade.

O score de risco ARISCAT é específico para CPPO e pode guiar a tomada de decisão para reduzir o risco de CPO, encorajando estratégias preventivas.

Várias CPPO, como atelectasia, pneumonia, pneumonite por aspiração e a síndroma de distress respiratório agudo (SDRA) são causadoras frequentes de IRAPO, independentemente do estado pré-cirúrgico do doente, porém outras causas clínicas são comuns na sua génese: aspiração, edema pulmonar e embolia pulmonar. [7,8,9,10,11].

Intervir de forma preventiva no desenvolvimento de CPPO causadoras de IRAPO inclui de entre outras medidas a otimização pré-operatória das comorbilidades, cessação do tabagismo e correção da anemia, além de estratégias de ventilação protetora intraoperatória e manejo apropriado dos medicamentos bloqueadores neuromusculares.

Os doentes cujo estado geral está comprometido por outras afeções tais como doenças neurológicas, insuficiência renal, infeções, anormalidades hepáticas, desnutrição ou disfunção pulmonar, apresentam risco mais elevado de CPO porque essas condições exacerbam o stress cirúrgico. [12].

Em vários estudos publicados, a incidência, o impacto na sobrevida e os fatores associados ao aumento do risco de IRAPO, são variáveis, e em um dos primeiros inquéritos envolvendo mais de 7000 doentes submetidos a vários procedimentos

gastrointestinais, urológicos, ginecológicos e ortopédicos, a IRAPO exigindo ventilação mecânica após 24 horas ocorreu em apenas 0,8%. [13].

Mais recentemente, uma análise de 180.359 doentes submetidos a grandes procedimentos cirúrgicos em 128 hospitais Veterans Affairs e 14 hospitais privados dos Estados Unidos documentaram uma incidência de 3% de IRAPO (definida como ventilação mecânica além de 48 horas após a cirurgia ou necessidade de reentubação. [13] A mortalidade aos 30 dias foi de 27% para o grupo que desenvolveu IRA em comparação com apenas 1,4% para aqueles não o desenvolveram. Vinte e oito variáveis foram identificadas como estando associadas ao aumento do risco de IRAPO. Estas incluíram uma classe alta da American Society of Anesthesiologists Physical Status score (ASA PS), sepsis no pré-operatório, emergência em oposição ao procedimento eletivo, função renal pré-operatória alterada, história de tabagismo ou doença pulmonar obstrutiva crónica (DPOC) e idade mais avançada. O tipo de procedimento também impactou o risco, com a maior incidência de IRAPO associada à cirurgia do trato aerodigestivo superior, correção de aneurisma torácico ou toracoabdominal, cirurgia torácica e cirurgia gastrointestinal e hepatobiliar. [13]

De uma maneira geral, as estratégias de tratamento da IRAPO dirigem-se ao tratamento da causa da insuficiência e a restauração da função pulmonar, devendo todos os doentes cirúrgicos ser cuidadosamente avaliados antes da cirurgia, monitorizados de perto durante e após o procedimento e tratados agressivamente para prevenir ou corrigir a IRAPO.

A prevenção das CPPO geradoras de IRAPO é muito importante e é alcançada através da modificação de múltiplos fatores, incluindo educação do doente / família, controle da dor e fisioterapia, de entre muitas outras medidas, reforçando o conceito basilar da medicina perioperatória que inclui a necessidade de uma vigilância pós-operatória, tanto mais intensa quanto maior o risco individual do doente. [14, 15,16,17,18]

Este capítulo pretende abordar a consequência mais grave do compromisso respiratório no período perioperatório, a IRAPO, efetuando uma revisão dos seus aspetos fisiopatológicos, clínicos e terapêuticos mais relevantes.

2. CONCEITO

2.1 Insuficiência Respiratória Aguda

In latu sensu, define-se insuficiência respiratória aguda (IRA), como a perda da capacidade de ventilar adequadamente ou fornecer oxigénio suficiente ao sangue e órgãos sistêmicos, sendo que o sistema respiratório não é mais capaz de atender às demandas metabólicas do organismo em relação à oxigenação do sangue e / ou eliminação de dióxido de carbono (CO_2).

2.2 Insuficiência Respiratória Aguda Pós-operatória

In latu sensu, define-se insuficiência respiratória aguda pós-operatória (IRAPO), como alterações das trocas gasosas que se apresentam após um procedimento cirúrgico e como resultado das mudanças induzidas pela anestesia e cirurgia.

A gravidade pode variar de hipoxemia transitória no período pós-operatório precoce até a forma mais letal, normalmente tardio sob a forma de SDRA.

De acordo com o recente consenso internacional sobre SDRA, a IRAPO pode ser classificada como leve (PaO_2 / FIO_2 > 200 mmHg e ≤ 300 mmHg), moderada (PaO_2 / FIO_2 > 100 mmHg e ≤ 200 mmHg), ou grave (PaO_2 / FIO_2 ≤100 mmHg).

3. CLASSIFICAÇÃO

De uma maneira geral a insuficiência respiratória (IR) pode ser classificada de acordo com os seguintes critérios:

A. Duração e natureza dos mecanismos de compensação

- aguda: rápida deterioração da função respiratória
- crónica: instalação progressiva (meses ou anos)
- crónica agudizada: insuficiência respiratória aguda sobreposta a insuficiência crónica

B. Mecanismo fisiopatológico envolvido:

Tipo 1 (hipoxémica)

Pressão parcial de oxigénio no sangue arterial (PaO_2) <60 mmHg (8.0 kPa) a ar ambiente. Geralmente observada em doentes em edema agudo de pulmão ou lesão pulmonar aguda. Esses distúrbios interferem na capacidade do pulmão de oxigenar o sangue à medida que ele flui pela vasculatura pulmonar.

Tipo 2 (Hipercápnica/Ventilatória)

Pressão parcial de dióxido de carbono no sangue arterial ($PaCO_2$)> 50 mmHg (6.7 kPa) (se não for um retentor crónico de CO_2). É geralmente vista em doentes com um aumento do trabalho respiratório devido à obstrução ao fluxo aéreo ou diminuição da complacência do sistema respiratório, com diminuição da força muscular respiratória devido a doença neuromuscular ou com insuficiência respiratória central e diminuição do drive respiratório.

Tipo 3 (Perioperatória)

Representa geralmente um subconjunto da insuficiência respiratória do tipo 1, porém às vezes é considerada separadamente porque é muito comum.

Tipo 4 (Choque)

Secundária à hipoperfusão dos músculos respiratórios na síndrome clinica de choque por instabilidade cardiovascular.

4. ETIOLOGIA

A IRA pode resultar de uma variedade de etiologias, de entre patologias pulmonares primárias ou por patologia extrapulmonar.

4.1 Causas multifatoriais

Anormalidades de vários sistemas orgânicos podem causar IRA:

- Sistema nervoso central (SNC): [(drogas, encefalopatia metabólica, infeções do SNC, aumento da pressão intracraniana (PIC), apneia obstrutiva do sono (AOS), hipoventilação alveolar central, medula espinhal (trauma, mielite transversa)]
- sistema neuromuscular (poliomielite, tétano, M. Gravis, Guillain-Barré, cuidados intensivos ou miopatia esteroide)
- parede torácica (cifoescoliose, obesidade)
- vias aéreas superiores (obstrução de aumento de tecido, infeção, massa; paralisia das pregas vocais, traqueomalácia)
- vias aéreas inferiores (broncospasmo, Insuficiência cardíaca congestiva, infeção)
- parênquima pulmonar (infeção, doença pulmonar intersticial)
- sistema cardiovascular

4.2 Insuficiência Respiratória Tipo 3 (Perioperatória)

A IRA é comum no período pós-operatório, sendo a atelectasia a sua causa mais frequente. Outras causas correntes de IRAPO independentemente do estado pré-cirúrgico do doente podem incluir a pneumonia, pneumonite por aspiração, edema pulmonar e embolia pulmonar. A IRA secundária à disfunção cardíaca é excluída do conceito de IRAPO.

Assim, as medidas para reverter as atelectasias são primordiais.

Em geral, os efeitos residuais da anestesia, a dor pós-operatória e a alteração da mecânica toraco-abdominal contribuem para diminuir a capacidade residual funcional (CRF), condicionando o colapso progressivo das unidades pulmonares dependentes.

Podem incluir-se dentre as causas mais frequentes de atelectasia pós-operatória:

- diminuição de CRF
- decúbito dorsal / obesidade / ascite
- anestesia
- incisão abdominal superior
- secreções das vias aéreas

5. SINAIS CLÍNICOS E SINTOMAS

As manifestações clínicas do desconforto respiratório associado a IRA refletem sinais e sintomas de hipoxemia, hipercapnia ou o aumento do trabalho respiratório necessário.

Esses incluem:

- Estado mental alterado (agitação, sonolência)
- Cianose periférica ou central ou diminuição da saturação de oxigénio na oximetria de pulso
- Manifestações de uma "resposta ao stress", incluindo taquicardia, hipertensão e diaforese
- Evidência de aumento do trabalho respiratório, incluindo uso de musculatura acessória, flaring nasal, indução de movimentos intercostais, retrações supraesternais ou supraclaviculares, taquipneia
- Evidência de fadiga diafragmática (paradoxo abdominal)
- Resultados anormais de gases no sangue arterial

6. AVALIAÇÃO DIAGNÓSTICA DA ETIOLOGIA DA HIPOXEMIA E DA HIPERCAPNIA

O diagnóstico sindrómico envolve a identificação de sinais e sintomas e deve sempre ser confirmado laboratorialmente, através da gasometria arterial.

6.1 Avaliação de hipoxemia

O primeiro passo para identificar o mecanismo responsável pela hipoxemia envolve a determinação da diferença alvéolo-arterial de O_2, a D (A – a) de O_2, medida indireta do distúrbio V/Q. A D (A – a) de O_2 é determinada pela equação do gás alveolar:

$PAO_2 = PiO_2 – (PaCO_2/RQ)$

Onde, PAO_2 é a pressão alveolar de O_2, PiO_2, a pressão inspirada de O_2, $PaCO_2$, a pressão arterial de CO_2, e RQ, o quociente respiratório, definido como a razão entre a produção de CO_2 e o consumo de O_2 (VCO_2/VO_2). A Pi é uma função da FiO2, da pressão barométrica (PB) e da pressão parcial do vapor d'água no gás umidificado (PH_2O). Assim, $PiO_2 = FiO_2 \times (PB – PH_2O)$. Na temperatura corporal a PH_2O é 47 mmHg. Num indivíduo saudável, respirando ar ambiente ao nível do mar, onde $FiO_2 = 0,21$, PB = 760 mmHg, $PaO_2 = 90$ mmHg, $PaCO_2 = 40$ mmHg, e RQ = 0,8, temos:

$PAO_2 = PiO_2 – (PaCO_2/RQ)$
$= FiO_2 \times (PB – PH_2O) – (PaCO_2/RQ)$
$= 0,21 \times (760 – 47) – (40/0,8)$
= 100 mmHg

Se $PaO_2 = 90$ mmHg, então a D (A – a) de O_2, nesta condição ideal, é 10 mmHg. A D (A – a) de O_2 normal, entretanto, varia com a idade. Tomando como exemplo um doente admitido numa unidade de cuidados intensivos (UCI) que tenha mais de 40 anos, respirando ar ambiente, a D (A – a) de O_2 pode chegar a 25 mmHg.

A FiO_2 também influencia o valor da D (A – a) de O_2. Para cada acréscimo em 10% na FiO2, a D (A – a) O_2 aumenta 5 a 7 mmHg, chegando a 60 mmHg com O_2 puro. A explicação baseia-se no conceito de que altas FiO_2 resultam em perda do mecanismo de vasoconstrição hipóxica regional, levando, inadvertidamente, a aumento de fluxo sanguíneo em áreas pouco ventiladas. Isto ocasiona aumento da fração de shunt e consequente aumento da D (A – a) de O_2. O doente em UCI, recebendo O_2 suplementar, pode ter, portanto, valores de D (A – a) de O_2 bastante elevados. Depois de corrigir a D (A – a) de O_2 para a idade e FiO_2, a interpretação da D (A – a) de O_2 é a seguinte:

1. D (A – a) de O_2 normal: indica a hipoventilação como mecanismo responsável pela hipoxemia. Geralmente, na UCI, as causas mais comuns são depressão do drive respiratório induzida por drogas e fraqueza neuromuscular. Esta última pode ser reconhecida pela medida da pressão inspiratória máxima (Pimax).
2. D (A – a) de O_2 aumentada: indica distúrbio V/Q e/ou desequilíbrio oferta/consumo (DO_2/VO_2) como mecanismos para hipoxemia. Nesta situação, é necessária a medida da PvO_2 (central ou mista) para identificar a presença desse desequilíbrio.

A medida da PvO_2 só se aplica aos doentes que possuírem cateter venoso central ou cateter de artéria pulmonar. Interpreta-se o valor da PvO_2 do seguinte modo:

1. PvO_2 normal: indica que se trata de distúrbio V/Q. PvO_2 maior ou igual a 40 mmHg coloca os pulmões como fonte da hipoxemia.
2. PvO_2 baixa: valores de PvO_2 abaixo de 40 mmHg apontam para existência de desequilíbrio DO_2/VO_2 (baixa DO_2 ou alto VO_2).

6.2 Avaliação da Hipercapnia

O nível de CO_2 no sangue arterial ($PaCO_2$) é diretamente proporcional à taxa de produção pelo metabolismo oxidativo (VCO_2) e inversamente proporcional à taxa de eliminação pela ventilação alveolar (VA). Assim, $PaCO_2 = k \times (VCO_2/VA)$, onde que é uma constante de proporcionalidade. A VA se refere à fração do

volume expiratório total que não é espaço morto (Vd/Vt), ou seja, VA = VE × (1 – Vd/Vt). Portanto:

$PaCO_2 = k \times [VCO_2/VE \times (1 – Vd/Vt)]$

Esta equação revela três fatores causais para hipercapnia: aumento da produção de CO_2 (VCO_2), hipoventilação (VE) e aumento do espaço morto (Vd/Vt). O aumento da produção de CO_2 é acompanhado por aumento na ventilação minuto, de forma que, normalmente, não resulte em hipercapnia. Na presença de espaço morto, entretanto, pode levar a aumento da $PaCO_2$.

A avaliação diagnóstica da etiologia da hipercapnia segue o mesmo raciocínio utilizado para a hipoxemia. A avaliação começa com o cálculo da D (A – a) de O_2. O encontro de D (A – a) de O_2 aumentada indica aumento no espaço morto. D (A – a) de O_2 normal aponta para a presença de hipoventilação alveolar.

A produção de CO_2 em condições normais, a taxa de eliminação de CO_2 é equivalente à VCO_2 e pode ser aferida pela calorimetria indireta. A VCO_2 normal varia de 90 a 130 L/min e corresponde a 80% do VO_2.

O aumento na VCO_2 pode ser causado por hipermetabolismo ou hiperalimentação. Esta última é causa importante de hipercapnia em doentes com doença pulmonar grave e IRA, especialmente quando em ventilação mecânica (VM), podendo causar atraso no processo de desmame.

A hipoventilação alveolar em cuidados intensivos tem habitualmente duas causas comuns: depressão respiratória induzida por drogas e fraqueza neuromuscular. A medida da Pimax é o método padrão para avaliar a força da musculatura respiratória. Pode ser aferida quando há esforço inspiratório máximo contra válvula fechada. A Pimax varia com a idade e o sexo. Indivíduos saudáveis apresentam valores de Pimax maiores do que 80 cmH_2O. Desenvolve-se hipercapnia quando o valor da Pimax cai para menos de 40% do normal.

6.3 Achados do Raio-x do tórax

Embora não patognomónicos no diagnóstico de IR aguda, a avaliação do raio-x do tórax revela-se de grande importância, sobretudo em termos etiológicos. De uma maneira geral os seguintes achados radiológicos podem polarizar-nos para as seguintes etiologias, sobretudo quando associados a clinica e ao laboratório:

- Radiografia torácica clara com hipoxemia e normocapnia - Embolia pulmonar, Shunt direita-esquerda, Choque
- Radiografia torácica difusa (opacificada) com hipoxemia e normocapnia - SDRA, Edema pulmonar de origem não cardíaca, insuficiência cardíaca congestiva (ICC), fibrose pulmonar
- Infiltrado localizado - pneumonia, atelectasia, infarto
- CXR clara com hipercapnia - DPOC, asma, overdose, fraqueza neuromuscular

6.4 Achados da Ecografia torácica

A ultrassonografia do tórax pode dar-nos um diagnóstico preciso das condições que comumente causam IRA e pode melhorar a precisão geral do diagnóstico em ambientes de cuidados intensivos em comparação com as abordagens de diagnóstico padrão. Os médicos que trabalham em unidades de cuidados intensivos estão a tornar-se cada vez mais familiarizados com a ultrassonografia como parte da prática clínica de rotina, embora a maioria dos dados até o momento se tenha concentrado em cenários de emergência e terapia intensiva.

Existe forte evidência no uso do ultrassom diagnóstico de tórax, com foco em diferentes níveis de eficácia de imagem; especificamente atributos do teste de ultrassom, impactos no comportamento clínico e até impacto nos resultados.

P. Wallbridge et al. [19] sumarizam na Tabela 1, a seguir representada, as características diagnósticas da ultrassonografia torácica para etiologias comuns da IRA.

Tabela 1: Características diagnósticas da ultrassonografia torácica param etiologias comuns da IRA

Pneumothorax [19–22]	Absent lung sliding	Lung bullae	88% (85–91) [19]	99% (98–99%) [19]	Studies typically in trauma (high prevalence)
	Absence of B-lines	Localised fibrosis	91% (86–94) [20]	98% (97–99%) [20]	Heterogeneity on meta-analysis
	Lung-point	ARDS	79% (68–98) [21]	98% (97–99) [21]	
	'Stratosphere sign'	Mainstem intubation	87% (81–92%) [22]	99% (98–99) [22]	Clinical significance of pneumothorax not detected on CXR unclear
	Ruled out by presence of 'lung pulse'				
Pleural effusion [36,37]	Hypoechoic space: 'quad sign'	Pleural thickening	93% (89–96) [36]	96% (95–98) [36]	High prevalence of effusion in included studies
	'Sinusoid sign'	Intra-parenchymal fluid	94% (88–97) [37]	98% (92–100) [37]	
Pneumonia [41,45–47]	Increased echogenicity	Atelectasis	*All comers:*	*All comers:*	Studies report high prevalence of pneumonia (clinical context important)
	Loss of pleural line	Pulmonary infarction	97% (93–99) [45]	94% (85–98) [45]	
	Air-bronchograms	Pulmonary contusion	94% (92–96) [46]	96% (94–97) [46]	
	Hypo-echoic/serrated distal edge	Neoplasm	95 (93–97) [47]	90% (86–94) [47]	Sensitivity of US in ARF depends on unit of analysis (per patient or per region) [41]
	Hypoechoic vascular structures		*ARF:* 91% (81–97) to 100% (95–100) [41]	*ARF:* 78% (52–94) to 100% (99–100) [41]	
Pulmonary embolism [50,51]	Peripheral wedge-shaped consolidation	Pneumonia	87% (76–92) [50]	82% (71–89) [50]	Poor performance as both 'rule-in' and 'rule out' test [51]
	Lower limb DVT	Neoplasm	85% (78–90) [51]	83% (73–90) [51]	
	Right ventricular dysfunction				
	Pleural effusion				
Pulmonary oedema and interstitial lung disease (ILD) [67,68]	Increased B-lines ("interstitial syndrome")	*Diffuse:* Cardiogenic pulmonary oedema, ARDS, Infection, Interstitial lung disease	*Cardiogenic pulmonary oedema:* 94% (81–98) [67] 85% (83–88) [68]	*Cardiogenic pulmonary oedema* 92% (84–96.) [67] 93% (91–94) [68]	Poorly predicts pulmonary occlusion pressure [37]
		Non-cardiogenic pulmonary oedema	*Non-cardiogenic pulmonary oedema/ ILD:*	*Non-cardiogenic pulmonary oedema/ ILD:*	Predicts extravascular lung water [37–39]
		Focal: Pneumonia, pulmonary contusion, fibrosis, lymphangitis	N/A	N/A	
Diaphragm dysfunction [79,81,82]	Reduced thickness	Direct trauma	N/A	N/A	Thickening ratio has modest predictive value for weaning outcome, with lower accuracy for excursion [87].
	Reduced thickening ratio	Surgery			
	Reduced/paradoxical excursion	Adjacent consolidation, malignancy or atelectasis			
		Fluid (pleural/ascites)			
		COPD			
		Neuromuscular disease			
		Denervation (neck/chest)			

Abbreviations; ARDS – acute respiratory distress syndrome; ARF – acute respiratory failure; COPD – chronic obstructive pulmonary disease; CXR – chest x-ray; US - ultrasound.

[a] Reported by systematic reviews.

7. TRATAMENTO DA INSUFICIÊNCIA RESPIRATÓRIA AGUDA

7.1 Atelectasia enquanto causa frequente de IRA tipo III

7.1.1 Medidas gerais de reversão

- Virar o doente com a periodicidade de 1-2 h
- Fisioterapia respiratória
- Espirometria de incentivo
- Tratamento da dor incisional (pode incluir anestesia peridural ou analgesia controlada pelo doente)
- Ventilar a 45 graus na posição vertical
- Drenagem adequada de interposições líquidas pleurais e abdominais (derrame pleural e ascite)
- Reexpansão do colapso pulmonar
- Evitar a sobrecarga hídrica

O manejo da IR aguda pode ser dividido em uma fase de ressuscitação urgente seguida por uma fase de atendimento contínuo.

O objetivo da fase de ressuscitação urgente é estabilizar o doente o máximo possível e evitar qualquer deterioração que ameace a vida. Uma vez que esses objetivos sejam alcançados, o foco deve ser direcionado para o diagnóstico do processo subjacente e, em seguida, a instituição da terapia deve estar voltada para reverter a etiologia primária do IR aguda.

7.1.2 Ressuscitação urgente

- Oxigenação
- Controle das vias aéreas
- Suporte ventilatório mecânico se indicado
- Estabilização da circulação
- Broncodilatadores / Esteroides

7.1.3 Cuidados contínuos

- Diagnóstico diferencial e investigações
- Plano terapêutico adaptado ao diagnóstico

O suporte respiratório da IRAPO pode incluir de entre outras medidas a seguintes: oxigeno terapia, ventilação mecânica por pressão positiva invasiva e não invasiva e fisioterapia.

A) Oxigenação

Quase todos os pacientes com IRA necessitam de oxigénio suplementar. Todos devem ser colocados em um oxímetro de pulso e a saturação de oxigénio geralmente deve ser mantida acima de 90%.

O oxigénio difunde-se do alvéolo através da membrana alveolar para o sangue capilar. A taxa de difusão é impulsionada pelo gradiente de pressão parcial de oxigénio. Portanto, aumentar o PAO_2 com oxigénio suplementar deve melhorar a transferência de oxigénio para o sangue capilar pulmonar.

Existem vários dispositivos diferentes que podem ser usados para fornecer oxigénio. Eles diferem em termos de sistemas abertos ou fechados, se fornecem concentrações de oxigénio baixas ou altas, e se são sistemas de fluxo baixo ou

alto. A sua eficácia depende se eles podem fornecer oxigénio suficiente a uma taxa de fluxo suficiente para atender às demandas dos doentes.

Doentes não intubados respirando espontaneamente através de um sistema aberto "arrastam" algum ar ambiente de seu ambiente a cada respiração. Assim, a concentração final de oxigénio fornecida a eles dependerá de quanto foi distribuído pelo dispositivo de oxigénio e quanto foi o ar ambiente arrastado. Quanto mais baixo o fluxo liberado pelo dispositivo de oxigénio, e quanto maior for o fluxo inspiratório do doente, mais espaço ele será arrastado, resultando em uma menor concentração de oxigénio. Por exemplo, um doente taquipneico provavelmente terá um drive respiratório alto e altos fluxos inspiratórios. Ele exigirá um sistema de alto fluxo para evitar o arrastamento significativo de ar ambiente e, assim, a diluição do oxigénio liberado.

A.1 Cânula nasal

Baixo fluxo, baixa concentração de oxigénio, dispositivo aberto.

O oxigénio a 100% é fornecido através de cânulas a 0,5 a 6 l / min. Maiores taxas de fluxo não aumentam significativamente a FIO_2 e levam à secagem da mucosa e ao desconforto do doente. A FIO_2 resultante depende da ventilação por minuto do doente e da quantidade de ar ambiente que é arrastado. Assim, não pode ser controlado com precisão. A concentração máxima de oxigénio na traqueia não deve exceder 40 a 50%. Os óculos nasais são geralmente usados para doentes relativamente estáveis que não necessitam de FIO_2 elevado ou controle preciso de sua FIO_2.

A.2 Máscaras de Venturi

Estas são concentrações variáveis de oxigénio, fluxo baixo a moderado, dispositivos abertos. Essas máscaras de entrada de ar fornecem 100% de oxigénio através de um dispositivo de mistura a jato que causa um arraste controlado de ar e, assim, permite a entrega de concentrações precisas de oxigénio de 24 a 60%. Essas máscaras são úteis em doentes com DPOC nos quais uma titulação precisa da concentração de oxigénio pode ser desejável para minimizar o aumento da PCO_2.

A.3 Máscaras de reservatório

Estes são dispositivos abertos de alto fluxo de oxigénio, projetados para minimizar o arrastamento de ar em doentes com alta demanda de fluxo inspiratório. Essas máscaras incorporam uma bolsa reservatório que é preenchida com oxigénio a 100%. Se o doente fizer um esforço inspiratório, gerando um fluxo maior do que o circuito da parede pode fornecer, o reservatório de oxigénio será esvaziado para minimizar o arrastamento do ar ambiente. O uso de "presas" na máscara facial é um princípio semelhante. A bolsa deve estar pelo menos parcialmente distendida durante todo o ciclo respiratório.

A.4 Unidade de Ressuscitação Bolsa-Máscara-Válvula

Alto oxigénio, dispositivo de alto fluxo. O fluxo de oxigénio deve ser mantido alto (15 l / min) quando este dispositivo for usado. Quando a máscara é mantida firmemente sobre a face com uma boa vedação da máscara facial, o arrastamento do ar ambiente é minimizado.

A.5 Ventilação por Pressão Positiva Não Invasiva (VPPNI)

A NPPV fornece assistência ventilatória, pressão positiva e uma concentração controlada de oxigénio usando uma máscara facial justa como a interface entre o doente e o ventilador, em vez de um tubo endotraqueal. Pode ser usado para evitar ou impedir a intubação em doentes cuidadosamente selecionados.

A NPPV aplicada principalmente no edema pulmonar cardiogénico, na DPOC descompensada e na insuficiência pulmonar hipoxémica, também é usada atualmente em ambientes perioperatórios. Apesar desses dados limitados e da necessidade de novos ensaios randomizados, a NPPV pode ser considerada uma ferramenta profilática e terapêutica para melhorar a troca gasosa em doentes no pós-operatório [20,21,22].

A.6 Ventilação mecânica invasiva por pressão positiva

A potencial gravidade da IRAPO poderá necessitar de recurso a ventilação mecânica invasiva (VIPP), cuja abordagem do ponto de vista de programação genérica, potenciais complicações e efeitos adversos serão objeto de abordagem em outro capítulo da presente secção.

8. FISIOTERAPIA RESPIRATÓRIA

O racional para o uso fisioterapia respiratória no período pós-operatório assenta no facto de que, de um modo geral as cirurgias, em particular as cirurgias abdominais causam limitações no fluxo respiratório e alteram a força dos músculos envolvidos na respiração, o que leva a restrição funcional e dolorosa, alterando a mecânica respiratória, per si geradora de insuficiência respiratória perioperatória.

Além disso, os períodos prolongados de imobilismo decorrente da restrição ao leito, a presença de drenos e pensos, também contribuem para disfunções respiratórias e motoras. Diante disso, é consensual a necessidade de cuidados especiais no período pós-operatório, sendo a fisioterapia um recurso de importância reconhecida na prática clínica para este fim.

Existe comprovada evidências científicas relacionadas a atuação fisioterapêutica nos acometimentos respiratórios e motores de doentes pós-operados, sendo que a fisioterapia respiratória é importante na recuperação e prevenção de complicações no pós-operatório, visto que há uma perda da função pulmonar decorrente dos fatores já mencionados (manipulação abdominal, período cirúrgico, tempo prolongado no leito, dor no local da incisão e resíduos anestésico) [23].
Para realização da fisioterapia, uma prévia avaliação do doente, considerações sobre sua clínica e o conhecimento das indicações e contraindicações das manobras fisioterapêuticas no período pós-operatório são imprescindíveis [24].

Diversas técnicas, manuais e mecânicas, são utilizadas nesses casos com objetivo de aumentar o volume pulmonar, diminuir o trabalho dos músculos da respiração, melhorar a ventilação e as trocas gasosas. O intuito final é tornar o mecanismo de respiração eficiente, sem gastos excessivos de energia, evitando-se complicações [25].
Particular desenvolvimento do tema será feito no capítulo específico da presente secção.

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5.7 Anexo VII: Documentos

1. Admissão ao 3º ciclo de doutoramento em Ciências Médicas

LARGO PROF. ABEL SALAZAR, 2. 4099-003 PORTO
TELEFONE : 351 22 206 22 00
FAX : 351 22 206 22 32
E-mail: aguas@icbas.up.pt

Exmo. Senhor
Dr. Antero do Vale Fernandes
Rua Martinho de Assunção n.º 34
2740-100 Porto Salvo-Oeiras

392 29 FEV. 2012

Porto, 25 de novembro de 2011.

Assunto: **Requisitos do Programa de Doutoramento em Ciências Médicas do ICBAS/UP.**

Caro Dr. Antero do Vale Fernandes – Proc. (secretariado) n.º 9/40 (3CCM)

Como diretor do Doutoramento em Ciências Médicas, do ICBAS/UP venho confirmar por escrito que a sua candidatura como estudante de doutoramento do ICBAS/UP foi formalmente aprovada pela Comissão Científica deste Programa.

Gostaria de lhe recordar que irá iniciar o seu Ano Probatório como estudante de doutoramento, o que significa que dentro de cerca de 12 meses lhe iremos solicitar para escrever um relatório das actividades realizadas no âmbito da investigação proposta, assim como uma apresentação oral do mesmo relatório que será sujeita a discussão e apreciação por um júri que incluirá o seu orientador e um membro da Comissão Científica do Doutoramento. Esta prova no final do período do Ano Probatório irá decidir a sua passagem para a situação de estudante definitivo de doutoramento do ICBAS/UP.

Queria agora comunicar-lhe que a Associação Europeia de Escola Médicas que se tem dedicado à criação de consensos sobre os requisitos de qualidade a exigir a teses de doutoramento em Ciências Médicas na Europa (associação denominada como ORPHEUS), considera que as teses só devem ser defendidas após o estudante ter três artigos científicos aceites para publicação internacional em revistas indexadas na Web of Knowledge, sendo que deverá ser primeiro autor de um desses artigos. A ORPHEUS postula ainda que no caso de o estudante publicar como primeiro autor um artigo em revista de impacto elevado (superior a 6), considerar-se-á que adquire o direito de ficar isento do cumprimento do requisito de ser autor de dois artigos adicionais. A ORPHEUS afirma ainda que é inadequado para as Ciências Médicas o requisito de obrigatoriedade de frequência de cursos monográficos, comum à maioria dos programas de doutoramento em outras áreas, já que os estudantes de doutoramento são por regra clínicos que exercem profissão em área pelo menos aparentada à do seu tema de doutoramento. A necessidade de formação adicional, de curso monográfico ou outra, no âmbito do programa de doutoramento ficará ao critério apenas do estudante ou do orientador científico da tese de doutoramento. A Comissão Científica do Doutoramento em Ciências Médicas, do ICBAS/UP aderiu a estes princípios.

Assim e de acordo com o Regulamento Geral dos Terceiros Ciclos de estudos da Universidade do Porto, o Programa de Doutoramento em Ciências Médicas do ICBAS/UP tem como requisito que a tese só poderá ser aceite para discussão pública após o estudante documentar que pelo menos parte da sua tese, já deu origem a três trabalhos científicos aceites para publicação (ou publicados), sendo pelo menos um deles como primeiro autor, em revistas científicas internacionais indexadas na Web of Knowledge do Institute for Scientific Information (USA).

Apresento-lhe os meus votos pessoais das maiores venturas na execução do seu Programa de Doutoramento e agradeço-lhe o ter escolhido o ICBAS/UP como instituição onde se propõe defender a sua tese de doutoramento.

Com os nossos cumprimentos,

Prof. Doutor Artur Águas
Diretor do Doutoramento em Ciências Médicas do ICBAS/UP

2. Regulamento Especifico de Doutoramento em Ciências Médicas

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

LARGO PROF. ABEL SALAZAR, 2. 4099-003 PORTO
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3º CICLO EM CIÊNCIAS MÉDICAS (3.º CDCM)

Regulamento Específico do Doutoramento em Ciências Médicas, do ICBAS/UP aprovado na Reunião de 21 de Abril de 2010, da Comissão Coordenadora do Conselho Científico:

1. Para que uma candidatura a aluno de doutoramento em Ciências Médicas, do ICBAS seja aceite é requerido que o orientador ou co-orientador do aluno documente historial sólido de publicação científica internacional.

2. A tese de doutoramento só será aceite para apreciação pela Comissão Científica do Programa após o aluno de doutoramento ter demonstrado ser autor, no âmbito do tema da tese, de pelo menos 3 artigos científicos aceites para publicação ou publicados em revistas internacionais indexados pela "Web of Knowledge" (a qual é da responsabilidade do Institute for Scientific Information).

3. Dos 3 artigos referidos no número anterior, o aluno de doutoramento terá que ser primeiro autor de pelo menos um desses artigos. No caso do aluno de doutoramento ser primeiro autor de artigo científico aceite para publicação ou publicado em revista de elevado impacto (superior a 6, de acordo com a Web of Knowledge) será isento do requisito de ser autor de 2 artigos científicos adicionais.

Prof. Doutor Artur Águas
Director do Curso

3. Base de dados eletrónica do II Trabalho original

Base de dados

- Factores de risco para complicações pulmonares
- Factores envolvidos na fisiopatologia das complicações respiratórias no pós-operatório
- Caracterização da Insuficiência respiratória
- Manuseio da Insuficiência respiratória

- http://www.anterofernandes.com

4. Resumo do relatório de atividades do ano probatório

3º Ciclo de Doutoramento em Ciências Médicas

Relatório de Actividades do ano probatório

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Antero Fernandes, MD, EDIC

ECTS obtidos: 60

Conclusão

- Cremos ter identificado durante o ano probatório as metodologias adequadas para a realização das actividades a que nos propusemos. Nas fases seguintes do programa doutoral, esperamos conseguir obter resultados que contribuam para uma melhor caracterização dos instrumentos de medição dos factores de risco e prognóstico de CPPO em doentes submetidos a cirurgia abdominal, antever a sua evolução para insuficiência respiratória e estabelecer com clareza os seus mecanismos preventivos. Pretendemos publicar os nossos resultados.

5. Informação de avaliação das atividades do 2º ano e 3º ano

3º CICLO DE DOUTORAMENTO EM CIÊNCIAS MÉDICAS

Risco peri-operatório em cirurgia digestiva oncológica abdominal. Os modelos de avaliação do risco cirúrgico na avaliação da capacidade preditiva de complicações e da mortalidade pós-operatórias em patologia digestiva oncológica.

RELATÓRIO DE ACTIVIDADES DO 2º ANO

Estudante: Licenciado Antero do Vale Fernandes
Orientador: Professor Doutor Lúcio José de Lara Santos

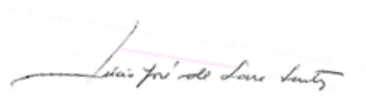
Largo Prof. Abel Salazar, 2. 4099-003 Porto
telefone + 351 22 206 22 00
fax + 351 22 206 22 32
Departamento de Patologia e Imunologia Molecular

INFORMAÇÃO

Informo, para os devidos efeitos, que o relatório do 2º ano apresentado pelo Estudante de Doutoramento Antero do Vale Fernandes, relativo ao trabalho de investigação conducente à elaboração da sua tese de doutoramento, cujo título era "**Factores de Risco para complicações pulmonares no pós-operatório de cirurgia geral. Validade de índice prognóstico para a a ocorrência de complicações pulmonares pós-operatórias**." Merece a minha aprovação. Com efeito, o projecto de investigação elaborado continua a manter toda a actualidade, está bem concebido e é exequível. Porém, a actividade realizada excede o título do da tese pelo que sugiro que esta seja alterada para "**Como mitigar o risco peri-operatório em cirurgia digestiva oncológica?**" As actividades programadas para o 2º ano foram cumpridas, o entusiasmo do estudante é crescente, as metas para os anos seguintes estão traçadas e tudo indica que venham a ser cumpridas no tempo previsto.

Assim sendo, sou de parecer que o relatório em análise elaborado pele Estudante de Doutoramento Antero do Vale Fernandes deva ser aprovado e que o título inicialmente proposto se mantenha.

O Orientador do Doutorando



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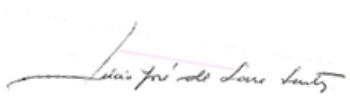
Departamento de Patologia e Imunologia Molecular

INFORMAÇÃO

Informo, para os devidos efeitos, que o relatório do 3º ano apresentado pelo Estudante de Doutoramento Antero do Vale Fernandes, relativo ao trabalho de investigação conducente à elaboração da sua tese de doutoramento, com o título "**Como mitigar o risco peri-operatório em cirurgia digestiva oncológica?**" Merece a minha aprovação. Com efeito, o projecto de investigação elaborado continua a manter toda a actualidade, está bem concebido e é exequível. A actividade realizada que incluiu um artigo em publicação, a participação no projecto da FCT e em congressos afins permite referir que as actividades do 3º ano foram cumpridas, o entusiasmo do estudante é crescente, as metas para o ano seguintes estão traçadas e tudo indica que venham a ser cumpridas no tempo previsto (após o interregno que foi obrigado a realizar e devidamente autorizado).

Assim sendo, sou de parecer que o relatório em análise elaborado pele Estudante de Doutoramento Antero do Vale Fernandes deva ser aprovado.

O Orientador do Doutorando



6. Comprovativo de submissão de Publicação Científica

Submission-ID: ERJ-03317-2020 "Outcomes of Acute Hypoxaemic Respiratory Failure. Insights from the Lung Safe Study"

"Outcomes of Acute Hypoxemic Respiratory Failure. Insights from the Lung Safe Study"

Full author list: Tai Pham, MD; Antonio Pesenti; Giacomo Bellani; Gordon Rubenfeld; Eddy Fan; Guillermo Bugedo; Jose Lorente; **Antero do Vale Fernandes**; Frank Van Haren; Alejandro Bruhn; Fernando Rios; Andres Esteban; Luciano Gattinoni; Anders Larsson; Danny McAuley; Marco Ranieri; Taylor Thompson; Herman Wrigge; Arthur S Slutsky; Laurent J. Brochard, MD; John Laffey

01-Sep2020

European Respiratory Journal

Outcomes of Acute Hypoxaemic Respiratory Failure.

Insights from the Lung Safe Study

Dear Prof. Brochard,

Thank you for your submission to ERJ. This email is to confirm that your article, entitled "Outcomes of Acute Hypoxaemic Respiratory Failure.
Insights from the Lung Safe Study", has passed the Admin checks and has been passed on to the Chief Editors for evaluation.

If you have any questions about this submission, please do not hesitate to contact me.

Kind regards,

Sarah Cleveland

European Respiratory Journal

Sarah.Cleveland@ersnet.org

7. Comprovativos de Editor do Tratado Lusófono de Terapia Intensiva, Coordenação da secão 5: Sistema respiratória e autoria de vários temas

TRATADO LUSÓFONO
DE MEDICINA INTENSIVA

Editores

Fernando Suparregui Dias
Rui Moreno
Ederlon Rezende
Antero Fernandes
Ciro Leite Mendes

Sumário

Versão 1.2 – Última atualização
25 de Maio de 2017

AMIB ASSOCIAÇÃO DE MEDICINA INTENSIVA BRASILEIRA

spci SOCIEDADE PORTUGUESA DE CUIDADOS INTENSIVOS

Atheneu

Seção 5 – Sistema respiratório

Coordenador : Antero Fernandes

48. Fisiologia respiratória e mecânica ventilatória ; Antero Fernandes, Paula Mendes

49. Trocas gasosas pulmonares e interação coração-pulmão : Miguel Tavares

50. Imagiologia do tórax no paciente crítico João Santos Silva,

51. Insuficiência respiratória por desordens específicas

55.1. SARA, Marcelo Amato

55.2. Asma aguda grave, João Gouveia

55.3. Doença pulmonar obstrutiva crônica exacerbada, Sergio Baldisseroto

55.4. Traumatismo de Crânio , Jacobo Bacariza, Rui Manilha

55.5 Traumatismo de Torax, Jacobo Bacariza, Nuno Cravalho

55.5. Perioperatória , Antero Fernandes, Lúcio Santos

56. Ventilação pulmonar artificial

56.1. Estado atual da ventilação mecânica Fernando Rua

56.2. Efeitos fisiológicos, repercussões hemodinâmicas e manifestações clínicas Edno Parolo

56.3. Indicações da ventilação mecânica: como iniciar, manter e controlar Ricardo Goulart

56.4. Modos convencionais de ventilação mecânica, Eliana Caser

56.5. Modos não convencionais de ventilação mecânica Jorge Valiatti

56.6. Manobras de recrutamento, Alexandre Biasi Cavalcanti

56.7. Tratamento da hipoxemia refratária: almitrina, óxido nítrico e posição prona, Antero Fernandes, Gonçalo Silva

56.8. Ventilação de alta frequência e ECMO Roberto Roncon

56.9. Ventilação não invasiva Carmen Silvia Valente Barbas

56.10. Descontinuação da ventilação pulmonar artificial Cassiano Teixeira

56.11. Complicações da ventilação mecânica Irene Aragão

56.12Broncofibroscopia para o intensivista- Chaves Caminha (POR)

56.13. Recursos Fisioterapêuticos durante a ventilação mecânica Miguel Gonçalves

56.14. A enfermagem na assistência ao doente em ventilação mecânica Albertina Gonçalves, José Serra

57. Broncoaspiração pulmonar Paulo Maia

58. Quase-afogamento Filipe Gonzalez, Vania Brito

TERMO DE CESSÃO
DE DIREITOS AUTORAIS
DE CAPÍTULO(S) PARA
LIVRO DE MEDICINA

Eu, Antero do Vale Fernandes, MD, EDIC, morador na rua Martinho de Assunção nº 34, Porto Salvo-Oeiras, de nacionalidade Portuguesa , portador do cartão de cidadão nº 13627383, com o telefone nº: + 351 91 8813307, cedo gratuitamente, em caráter irrevogável, os direitos autorais do(s) capítulo(s) de minha autoria cujos títulos são :

1. **Fisiologia respiratória e mecânica ventilatória** ; Antero Fernandes, Paula Mendes
2. **Tratamento da hipoxemia refratária**: almitrina, óxido nítrico e posição prona, Antero Fernandes, Gonçalo Silva
3. **Insufciência Respiratória Perioperatória**, Antero Fernandes, Paula Mendes, Lúcio Santos

Estes trabalhos virão integrar o **Tratado de Medicina Intensiva da AMIB – Associação Brasileira de Medicina Intensiva e SPCI – Sociedade Portuguesa de Cuidados Intensivos**, que tem como Editores os Professores: Fernando Suparregui Dias, Rui Moreno, Ederlon Rezende, Antero do Vale Fernandes e Ciro Leite Mendes.

Caberá à EDITORA ATHENEU sua publicação.

Ao ensejo, informo responsabilizar-me pelo teor do texto e a reprodução das imagens e fotos que irão constar em meu(s) capítulo(s).

São Paulo, 30 de Maio de 2019

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Célia Marta Pereira
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celiaeditorial@atheneu.com.br
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8. Pareceres

8.1. *Parecer da Comissão de Ética do Hospital Garcia de Orta-E.P.E sobre a realização de estudo basilar do ciclo de doutoramento*

Hospital Garcia de Orta, E.P.E.

DECLARAÇÃO

Para os devidos efeitos, declara-se que o Dr. Antero do Vale Fernandes submeteu à comissão de Ética do Hospital Garcia de Orta o Trabalho de Investigação denominado " **Factores de risco para complicações pulmonares no pós-operatório de cirurgia geral electiva não torácica. Validade de índice prognóstico para ocorrência de complicações pulmonares**", no âmbito do programa de doutoramento em ciências médicas em que se encontra inscrito no Instituto de Ciências Biomédicas Abel salazar da Universidade do Porto, tendo merecido parecer positivo desta comissão.

25/10/2011

O Presidente da Comissão de Ética

(Dr. Luis Antunes)

8.2. Parecer da Comissão de Ética sobre o Projeto de investigação "Stay home but stay strong", do qual resultou IV trabalho original enviado a publicação

Exmo. Senhor,
Profº. Doutor Lúcio Lara Santos
Grupo Patologia e Terapêutica Experimental do
Centro de Investigação
IPO Porto FG EPE

Ref. CES. 145/020
Porto, 02 de abril de 2020
Assunto: **Avaliação de Pedido de Parecer**

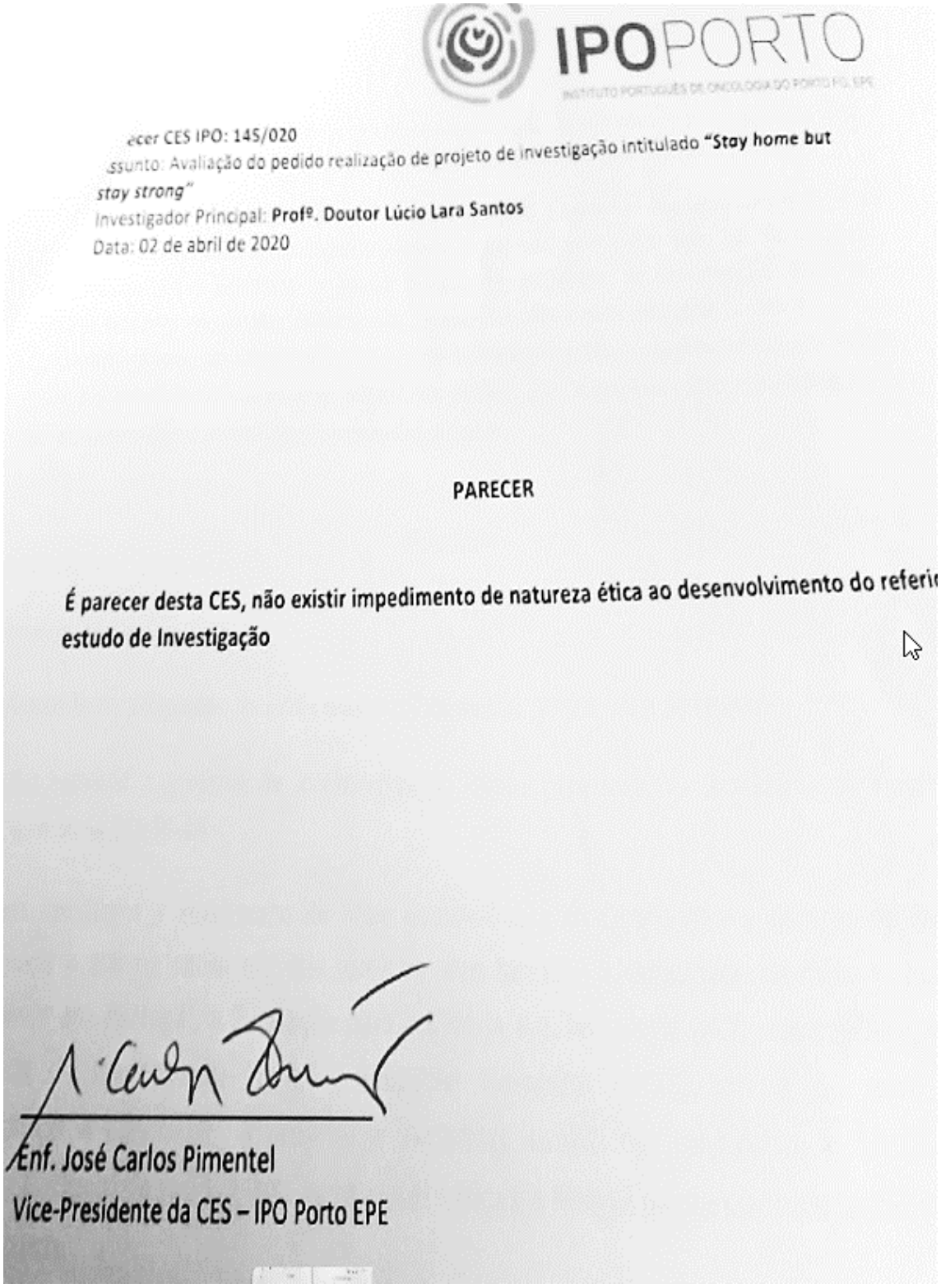
Exmo. Sr. Profº. Doutor Lúcio Lara Santos,

Cumpre-me remeter a V/Exa. o pedido de parecer dirigido a esta CES sobre o pedido de realização de projeto de investigação intitulado ***"Stay home but stay strong"****,* tendo como Investigador Principal o **Profº. Doutor Lúcio Lara Santos,** foi avaliado em reunião ordinária da Comissão de Ética a 02 de abril de 2020, emitindo-se o parecer anexo.

Respeitosos cumprimentos,

Enf. José Carlos Pimentel
Vice-Presidente da CES – IPO Porto EPE

UNIDADE INVESTIGAÇÃO CLÍNICA



IPOPORTO
INSTITUTO PORTUGUÊS DE ONCOLOGIA DO PORTO FG, EPE

ecer CES IPO: 145/020
ssunto: Avaliação do pedido realização de projeto de investigação intitulado **"Stay home but stay strong"**
Investigador Principal: **Profº. Doutor Lúcio Lara Santos**
Data: 02 de abril de 2020

PARECER

É parecer desta CES, não existir impedimento de natureza ética ao desenvolvimento do referi estudo de Investigação

Enf. José Carlos Pimentel
Vice-Presidente da CES – IPO Porto EPE

8.3. *Pareceres de submissão da tese de doutoramento a provas públicas*

Exmo. (a) Senhor (a)
Director (a) do Programa de Doutoramento em Ciências Médicas
Exmo. Senhor Professor Artur Águas

Lúcio José de Lara Santos, Professor Afiliado com Agregação do ICBAS , Orientador da tese de doutoramento intitulada: "**Como mitigar o risco perioperatório em cirurgia digestiva oncológica**", que tem vindo a ser realizada pelo estudante , Antero do Vale Fernandes , inscrito no curso de doutoramento em Ciências Médicas do ICBAS UP, declara, para os devidos efeitos, que o trabalho efectuado e conducente à tese de doutoramento se encontra em condições de ser submetido, brevemente, a provas públicas.

Porto, 10 de Setembro de 2020

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(*Assinatura*)

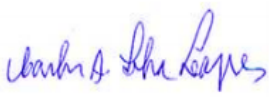
U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO
Departamento de Patologia e Imunologia Molecular

Rua de Jorge Viterbo Ferreira, 228 4050-313
PORTO
TELEFONE + 351 22 042 82 81
EMAIL: calopes@icbas.up.pt

Exmo. Senhor
Professor Doutor Artur Águas
Diretor (a) do Programa Doutoral em Ciências Médicas
ICBAS

Carlos Alberto da Silva Lopes , Professor Catedrático Jubilado do ICBAS, co-orientador da tese de doutoramento intitulada: ".**Como mitigar o risco perioperatório em cirurgia digestiva oncológica**..", que tem vindo a ser realizada pelo estudante , Antero do Vale Fernandes , inscrito no curso de doutoramento em Ciências Médicas do ICBAS UP, declaro, para os devidos efeitos, que o trabalho efectuado e conducente à tese de doutoramento se encontra em condições de ser submetido a provas públicas, para as quais pode ser admitido como está.

Porto, 10 de setembro de 2020



(Prof. Doutor Carlos Lopes)

Exmo. (a) Senhor (a)
Director (a) do Programa de Doutoramento em Ciências Médicas

Mário Dinis-Ribeiro, Professor Catedrático Convidado da Universidade do Porto , co-orientador da tese de doutoramento Intitulada: ".**Como mitigar o risco perioperatório em cirurgia digestiva oncológica**..", que tem vindo a ser realizada pelo estudante , Antero do Vale Fernandes , inscrito no curso de doutoramento em Ciências Médicas do ICBAS UP, declaro, para os devidos efeitos, que o trabalho efectuado e conducente à tese de doutoramento se encontra em condições de ser submetido, brevemente, a provas públicas.

Porto, 13 de Setembro de 2020

.....

(*Assinatura*)

9. Registos efetuados para elaboração da tese de doutoramento

U.PORTO

Boletim de Inscrição no Ensino Superior
Ano Letivo 2017/2018
INSCRIÇÃO EFETUADA COM SUCESSO

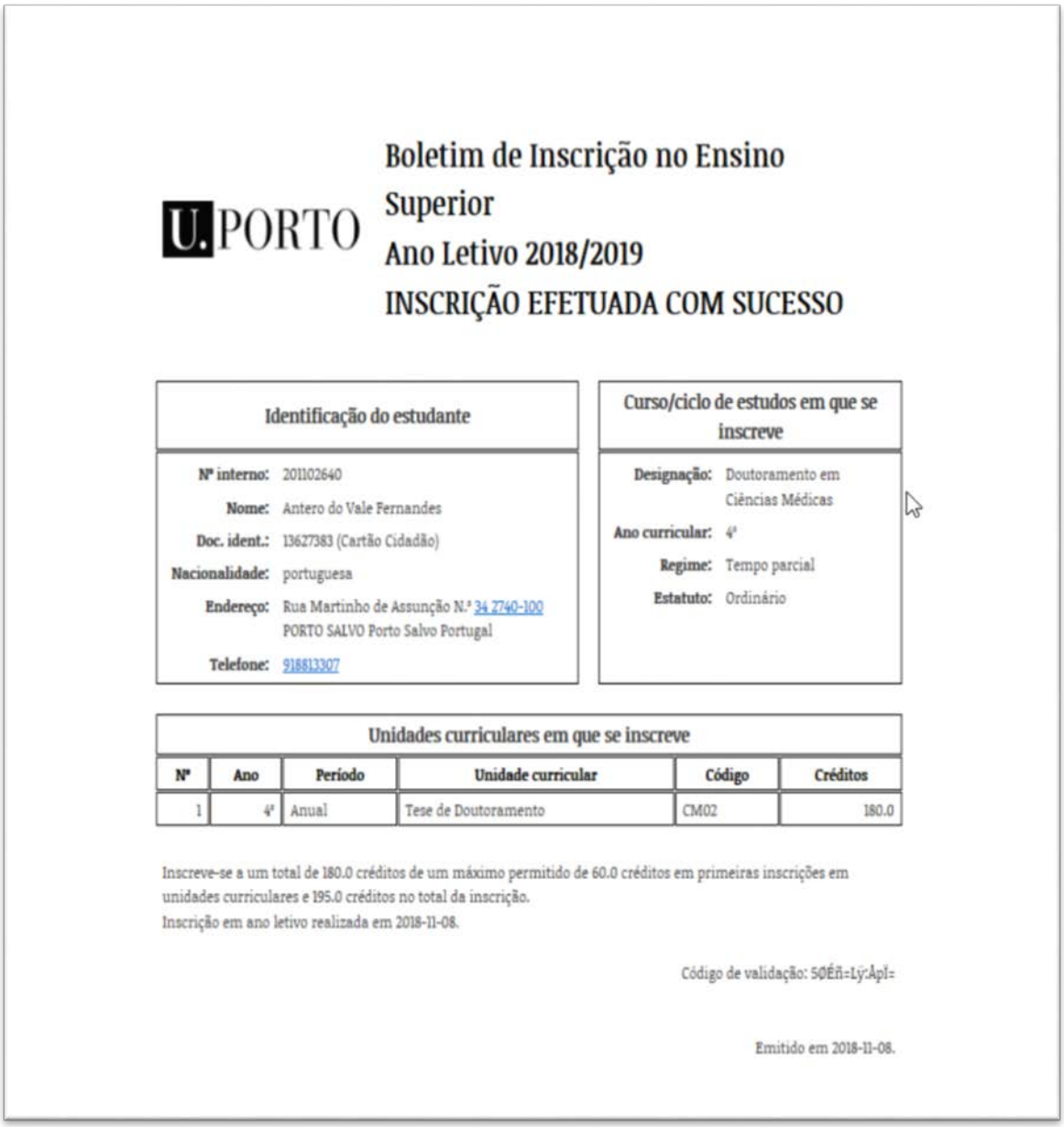
Identificação do estudante	
Nº interno:	201102640
Nome:	Antero do Vale Fernandes
Doc. ident.:	13627383 (Cartão Cidadão)
Nacionalidade:	portuguesa
Endereço:	Rua Martinho de Assunção N.º 34 2740-100 PORTO SALVO Porto Salvo Portugal

Curso/ciclo de estudos em que se inscreve	
Designação:	Doutoramento em Ciências Médicas
Ano curricular:	4º
Regime:	Tempo parcial
Estatuto:	Ordinário

Unidades curriculares em que se inscreve

Nº	Ano	Período	Unidade curricular	Código	Créditos
1	4º	Anual	Tese de Doutoramento	CM02	180.0

Inscreve-se a um total de 180.0 créditos de um máximo permitido de 60.0 créditos em primeiras inscrições em unidades curriculares e 180.0 créditos no total da inscrição.
Inscrição em ano letivo realizada em 2017-11-17.



U.PORTO

Boletim de Inscrição no Ensino Superior
Ano Letivo 2018/2019
INSCRIÇÃO EFETUADA COM SUCESSO

Identificação do estudante

Nº interno:	201102640
Nome:	Antero do Vale Fernandes
Doc. ident.:	13627383 (Cartão Cidadão)
Nacionalidade:	portuguesa
Endereço:	Rua Martinho de Assunção N.º 34 2740-100 PORTO SALVO Porto Salvo Portugal
Telefone:	918813307

Curso/ciclo de estudos em que se inscreve

Designação:	Doutoramento em Ciências Médicas
Ano curricular:	4º
Regime:	Tempo parcial
Estatuto:	Ordinário

Unidades curriculares em que se inscreve

Nº	Ano	Período	Unidade curricular	Código	Créditos
1	4º	Anual	Tese de Doutoramento	CM02	180.0

Inscreve-se a um total de 180.0 créditos de um máximo permitido de 60.0 créditos em primeiras inscrições em unidades curriculares e 195.0 créditos no total da inscrição.
Inscrição em ano letivo realizada em 2018-11-08.

Código de validação: 5ØÉñ=Lÿ:ÀpÍ=

Emitido em 2018-11-08.

3º Ciclo – Doutoramento em Ciências Médicas

Doctoral Programme in Medical Sciences

U.PORTO

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

EDIÇÃO 2011/2012 EDITION

Formulário de Proposta de Tese / Thesis Proposal Form

Using this Form, you can submit a project proposal to the Doctoral Programme when applying and before commencing the research project. You should consult and obtain the agreement of your supervisor(s) prior to submitting the proposal. Note that the Form is expandable, but please use only the amount of space that is strictly necessary, and do not use a text font other than Arial (9 point). The proposal will be reviewed by members of the Scientific Committee, and may be rejected or accepted (eventually in a provisional way). Please, submit the Form (in PDF format) with your application.

PROJECT INFORMATION (answer in ENGLISH or in PORTUGUESE)

Candidate Name: António do Vale Fernandes

Phone: 351 918813307

Email: antero.vf@netcabo.pt ; antervafe@gmail.com

Note: Please attach PDF copy of the CV (as in FCT-SIG database - http://www.fct.mctes.pt/fctsig/cv/# or in Europass CV)

PROPOSED SCIENTIFIC SUPERVISORS (maximum 3)

Supervisor: LÚCIO JOSÉ DE LARA SANTOS

Highest Degree: PhD

Institution: ICBAS - IPO-Porto

Category / Position: Professor Auxiliar Convidado

Phone: + 351 916331754

Email: llarasantos@gmail.com

Note: Please attach PDF copy of the CV (as in FCT-SIG database - http://www.fct.mctes.pt/fctsig/cv/# or in Europass CV)

Co-supervisor (if any): CARLOS SILVA LOPES

Highest Degree: PHD

Institution: ICBAS

Category / Position: Prof. Catedrático

Phone:

Email: lopes81241@gmail.com

Note: Please, attach PDF copy of the CV (as in FCT-SIG database - http://www.fct.mctes.pt/fctsig/cv/# or in Europass CV)

Co-supervisor (if any): MÁRIO JORGE DINIS RIBEIRO

Highest Degree: PhD

Institution: FMUP

Category / Position: Prof. Auxiliar com Agregação

Phone:

Email: mdinisribeiro@gmail.com

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Registo do tema de tese

Exmos.(as) Senhores(as) membros da Comissão Científica do Programa Doutoral em CIÊNCIAS MÉDICAS

Nome: António do Vale Fernandes

Estudante nº: 201102640

Vem requerer a V. Exª. autorização para o registo do seguinte tema de tese proposto nos termos do n.º 1 do artigo 12.º do *Regulamento Geral dos Terceiros Ciclos de Estudos da Universidade do Porto*:

COMO MITIGAR O RISCO PERI-OPERATÓRIO EM CIRURGIA DIGESTIVA ONCOLÓGICA?

(por favor preencher com letra maiúscula)

Para o efeito e de acordo com o n.º do já referido artigo, dá(ão) parecer favorável o orientador e coorientador(es) (se aplicável):

Orientador PROFESSOR DOUTOR LÚCIO LARA SANTOS
(por favor preencher nome completo)
Documento de Identificação n.º _____
Instituição ICBAS Categoria Professor Afiliado
Assinatura: _____ Data 19/6/2019

Coorientador PROFESSOR DOUTOR CARLOS ALBERTO DA SILVA LOPES
(se aplicável; por favor preencher nome completo)
Instituição ICBAS Categoria Prof. Catedrático Jubilado
Assinatura: _____ Data 19/6/2019

Coorientador _____
(se aplicável; por favor preencher nome completo)
Instituição _____ Categoria _____
Assinatura: _____ Data ___/___/____

Coorientador PROFESSOR DOUTOR MÁRIO DINIZ RIBEIRO
(se aplicável; por favor preencher nome completo)
Instituição EMUP Categoria Catedrático Convidado
Assinatura: _____ Data 19/6/19

Porto, ____de_____de 20_____

O(a) Estudante: António do Vale Fernandes

Recebido por: _____ em ___/___/_____

Legislação aplicável: Regulamento Geral dos Terceiros Ciclos de Estudos da U.Porto

“As to diseases, make a habit of two things
- to help, or at least, to do no harm“

Hippocrates

c. 460 - c. 370 aC

Médico grego da Era de Péricles (Grécia clássica)

O pai da medicina ocidental

“They always say time changes things, but you actually have to change them yourself”

Andy Warhol

1928- 1987

Artista, diretor e produtor americano

Porto, setembro de 2020

Antero do Vale Fernandes