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Costs of the Acute Respiratory Distress Syndrome

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Costs of the Acute Respiratory Distress Syndrome

By

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Abstract

The acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lungs and is a common condition in adult intensive care units (ICU). The resources required and costs of care for patients with ARDS are substantial due to the severity of illness, resource intensity and extended lengths of stay. There are two parts to this thesis: to systematically review the costing literature in ARDS and to perform a costing study of a cohort of patients with ARDS. The systematic review searched the literature through to April 29, 2021 for articles relevant to ARDS and costs. 4633 publications were found of which 110 were included for full-text review. A total of 22 publications met inclusion criteria and were kept for the final analysis. The assessment was done independently by two reviewers and the systematic review followed PRISMA guidelines. Quality assessment was done using a modified version of the Quality of Health Economic Studies Instrument. This review helped contextualize the results of the costing study. The aim of the costing study was to calculate both hospital inpatient costs and post discharge costs for the three years that followed for patients with ARDS. Clinical factors associated with costs during both the time periods were examined. The costing study was done on a cohort of 585 patients with ARDS who were prospectively identified using a standardized screening protocol in the 4 adults ICUs in Calgary, Alberta, Canada. The post discharge costs were calculated on 364 patients who survived their initial hospital stay and had a traceable, valid Alberta postal codes at the end of the three year follow-up period.

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List of Abbreviations

AB: Alberta
ABG: Arterial Blood Gas
ADBL: Alberta Drug Benefit List
AECC: American-European Consensus Conference
AHS: Alberta Health Services
AIC: Akaike Information Constant
ALC: Alternative level of care
ALI: Acute Lung Injury
ALTOS: ARDS Network Long-Term Outcomes Study
ANOVA: Analysis of Variance
APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
ARP: Alternative Relationship Plans
BRL: Brazilian Real
CACS: Comprehensive Ambulatory Classification System
CAD: Canadian Dollars
CADTH: Canadian Agency for Drugs and Technologies in Health
CCI: Canadian Classification of Health Interventions
CHEERS: Consolidated Health Economic Evaluation Reporting Standards
CI: Confidence interval
CIHI: Canadian Institute for Health Information
CLD: Chronic Liver Disease
CMDB: Canadian Management Information System Database
CMG: Case Mix Groups
CMS: Centers for Medicare and Medicaid Services
COPD: Chronic Obstructive Lung Disease
CSHS: Cost of a Standard Hospital Stay
D: Days
DAD: Discharge Abstract Database
D/C: Discharge
DRG: Diagnostic Related Groups
ECMO: Extracorporeal Membrane Oxygenation
ELOS: Expected Length of Stay
GBP: Great British Pounds
HFOV: High frequency oscillation ventilation
ICAP: Improving Care of Acute Lung Injury Patients
ICD-9: International Classification of Diseases, 9th edition
ICU: Intensive care unit
IHDA: Interactive Health Data Application
iNO: Inhaled nitric oxide
IQR: Interquartile Range
NARCS: National Ambulatory Care Reporting System

NHS: National Health Service
IQR: Interquartile range
LOS: Length of stay
MEPS: Medical Expenditure Panel Survey
MIS: Management Information System Database
MSE: Mean Squared Error
N/A: Not applicable
OHIP: Ontario Health Insurance Plan
OR: Odds ratio
PEEP: Positive end-expiratory pressure
P/F: $Pa0_2/Fi0_2$ ratio
PHN: Personal Health Care Number
PICOD: Population, Intervention, Comparator, Outcomes and Design
PIN: Pharmaceutical Information Network
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: Prospective Register of Systematic Reviews
QHES: Quality of Health Economic Studies
RIW: Resource intensity weight
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SD: Standard deviation
SE: Standard error
SOFA: Sequential Organ Failure Assessment
SS: Sum of squares
TISS: Therapeutic Intervention and Scoring System
US : United States
USD: United States Dollars
UK: United Kingdom

Chapter 1 - Background

1.1 Presentation and Diagnosis of ARDS

Acute Respiratory Distress Syndrome (ARDS) is an inflammatory condition of the lungs that was originally described in 1967[1]. In this publication, the authors reported a series of 212 patients with acute onset of tachypnea, hypoxemia, and loss of respiratory compliance resulting from a variety of underlying conditions such as trauma, pancreatitis and viral pneumonia.

ARDS is felt to be the result of an injury to the alveoli leading to diffuse alveolar damage[2]. This injury causes the release of cytokines and other mediators resulting in damage to the capillary and alveolar endothelium[3]. This, in turn, leads to proteinaceous fluid shifting into the interstitium and air spaces of the lung[4]. These pathological changes manifest clinically as decreased pulmonary compliance, impaired gas exchange and pulmonary hypertension[5-7].

Conditions that can cause ARDS are varied and are reflected in part, in the original description of the syndrome. They are often dichotomized into conditions that are direct pulmonary processes such as pneumonia, aspiration, contusion and inhalational injuries, and those that are secondary to extrapulmonary processes, such as sepsis, medication toxicities, transfusion reactions and pancreatitis[8]. The most common etiologies are pneumonia, aspiration and sepsis[9].

Standardizing criteria for the diagnosis of ARDS has been important in understanding the epidemiology and in advancing research into this condition. To this end, the American-European Consensus Conference definition was published in 1994[10]. The consensus criteria were: acute onset of bilateral infiltrates on a frontal chest radiograph, severe hypoxia defined as a $Pa0_2$ to $Fi0_2$ (P/F) ratio of < 300 mmHg, and with absence of left atrial hypertension. They classified a P/F ratio of 200-300 mmHg as Acute Lung Injury (ALI) and P/F ratio of < 200, mmHg as ARDS.

The American-European Consensus Conference criteria were criticized as they lacked an explicit definition of acute timing and were not sensitive to different ventilator settings. In addition, difficulties in ruling out congestive heart failure and the poor reliability of the chest radiograph criteria were considered other limitations[11]. The Berlin definition, another international consensus, was reached 18 years later[11]. These criteria improved upon the American-European Consensus Conference criteria by including timing, risk factors and degrees of severity (Table 1). The authors also included a series of clinical vignettes to clarify the radiographic criteria and to rule out hydrostatic edema as the primary cause of respiratory failure.

Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or worsening respiratory symptoms .
Chest Imaging	Bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules.
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present.
Oxygenation	
Mild	200 mmHg <P/F <= 300 with PEEP =>5 cm H_20
Moderate	100 mmHg < P/F <= 200 Hg with PEEP =>5 cm H_20
Severe	P/F <=100 mmHg with PEEP => 5 cm H_20

Table 1: The Berlin Definition of the Acute Respiratory Distress Syndrome[11]

P/F: $Pa0_2/Fi0_2$ ratio

PEEP: Positive End-Expiratory Pressure

1.2 Incidence of ARDS

Although the incidence of ARDS varies in the literature, it is a common problem in the population. The age adjusted incidence is reported to be between 27.6 and 86.2 cases per 100 000 person years[12, 13]. This variation may relate to location, as there appears to be a geographic variation in incidence, with the highest rates reported in the United States compared to other

developed countries[14]. Some variation may be related to the year of publication as the definition has changed over time. Older publications use the American-European Consensus Conference criteria and newer ones, the Berlin criteria. Furthermore, the use of standardised screening protocols and a focus on patients that sustain P/F ratio criteria over time may also contribute to this variation[12, 15]. An age-adjusted incidence of 86 per 100,000 person-years was found in a prospective study from the United States, using American-European Consensus Conference criteria without a screening protocol and based on a single measurement of the P/F ratio[13]. In contrast, a more recent publication from Alberta, Canada using a standardized screening protocol and the Berlin Criteria on sustained measurements, found an age adjusted incidence of 27.6 / 100 000 person years[12].

By extrapolation, using locally published incidence[12] and 2021 census data[16] we can expect approximately 890 cases per year in the Province of Alberta. Of note, all the available incidence data predates the emergence of Covid-19. The most common manifestation of severe disease is termed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), an important cause of ARDS[17]. Covid-19 has likely impacted the incidence of ARDS during the various waves of the pandemic[18] and what it will mean in its endemic state is not yet known[19].

1.3 Treatment and outcomes of ARDS

Most patients with ARDS require mechanical ventilation, making it a condition that is frequently encountered in intensive care units (ICU). The incidence amongst ICU admissions varies between 10 and 15%[12, 20, 21] and is associated with an overall mortality of approximately 40%[22]. Mortality increases with severity as defined by the Berlin criteria: mild 35 %, moderate 40 % and severe 46 %[23].

The treatment of ARDS is mostly supportive using low tidal volume ventilation[24], conservative fluid management[25], along with sedation and at times neuromuscular paralysis[26]. There is a role for prone positioning ventilation in patients with more severe disease[27] and some patient

require treatment with extra-corporal membrane oxygenation (EMCO)[28]. Treatment with inhaled vasodilators[29] and systemic corticosteroids[30] have been proposed with varied impacts reported on oxygenation, duration of mechanical ventilation and mortality. There have also been a number of investigational therapies that have been studied that have been proven to be ineffective or harmful[31].

1.4 Healthcare utilization and costs of ARDS

Patients with ARDS place significant demands on health care systems and ICUs in particular. The median ICU length of stay is 7.8 days (IQR 3.7, 14.3) and median duration of mechanical ventilation is 5.3 days (IQR 2.1, 10.8)[13]. The median hospital length of stay is 14 days (IQR 8.0, 24.0)[13]. The complexity of these patient and their resource use results in significant hospitalization costs[32]. ICU patients can contribute up to 10% of the total cost of inpatient care[33] with ARDS patients accounting for a disproportionate amount of these costs[34]. Studies report a wide range of costs per patient with ARDS, between $54 490 USD[35] and $450 888 USD[36]. This variability is in part explained by the context in which the study was undertaken with the least expensive in a publicly funded system in Finland[35] and the most expensive from a private hospital system in the United States[36].

This intense resource use is not isolated to the initial admission as survivors of ARDS continue to require significant health care services in the post-discharge period. Total mean costs at one year range from £29,171 GPB ($53,861 2021-USD)[37] to $115,400 USD (2010-USD).[38] The bulk of these costs are related to re-admissions to hospital following the initial hospitalization[39]. Readmission rates vary from 40%[40] to 45%[38] at one year, with a higher proportion occurring within 30 days after discharge[40]. Repeated admissions following discharge are common with one publication reporting a mean of 2.8 (SD 3.4)[38] readmissions at one year. Outpatient costs in the first year post discharge are also considerable and vary from a mean £3935 GBP ($7,266 2021-USD)[41] to $35,200 USD (2010-USD)[38]. Mortality is significant and ranges from 10%[40] to

45%[38] at one year. Survivors of ARDS also experience reductions in health-related quality of life, with both physical and psychological impairments that can persist for years[42].

It is notable that there is a limited amount of Canadian costing data reported in 3 publications[32, 43, 44], all from Ontario. One reports on post discharge costs only[44] and, of the two that report on inpatient costs, one predates the Berlin criteria in a cohort of 109 patients[32] and the other, from 2021 included 404 patients[43].

1.5 The impact of Covid-19

The impact of Covid-19 on health care costs has been significant[45]. Earlier in the pandemic, the risk of severe Covid infection, of which ARDS is the main manifestation, was as high as 5%[46], but this has dropped with the emergence of vaccines and less virulent variants[47]. While ARDS secondary to Covid-19 infection shares many of the same features as ARDS from other infectious causes, there have been mixed reports on differences in resource utilization as it pertains to duration of mechanical ventilation and ICU length of stay[48-50]. If differences truly exist, the impact they may have on resource utilization and costs is not yet known.

Chapter 2 - Accounting for Health Care Costs

2.1 Introduction

When evaluating health care costs, all relevant resources and services must be identified[51]. The relevance of each element is dependent on the perspective chosen for the evaluation. The perspective is the viewpoint from which the costs are to be evaluated and dictates what should be included in the analysis[52]. The Canadian Agency for Drugs and Technologies in Health (CADTH) outlines 4 economic perspectives[53]: Public Health Care Payer, Broader Government Payer, Private Payer, and Societal. When adopting the perspective of the Public Health Care Payer, only publicly funded costs are considered: some drugs and medical devices, hospital, physician, and diagnostic services, along with some community-based services such as home care and publicly funded rehabilitation and nursing homes. Any costs paid out of pocket by the patient or private insurer are excluded. The broader government perspective also includes other costs to government beyond health care, such as social services, affordable housing programs and education. The perspective of the Private Payer only includes the costs for medical supplies and services that they are covering, often only available outside of the public system. Examples are drugs and medical devices that are not covered through public funding, various aids and appliances, alternative care providers (chiropractic services, massage), other community based services, and private nursing homes. The broadest perspective is the Societal perspective. It includes all of the costs from the other perspectives but also takes into account any out of pocket expenses from the patient, such as insurance premiums, travel costs, informal caregiver costs, travel time, and lost wages[53]. Overall costs will vary by perspective with the societal perspective being higher given the breadth of costs considered[52]. Complexity in collecting economic data also varies with perspective; the use of databases to collect public payer costs is often more straightforward than collecting itemized out of pocket costs from patients[51].

2.2 Administrative Costing Data

Some economic evaluations track utilization and costs prospectively, but many capture data using administrative and clinical databases[51]. There are several sources of health costing data available to researchers and a number of them are often required to capture all relevant costs.

2.2.1 Institutional Databases

All publicly funded institutions in Canada track clinical activities by extracting data from patient charts at the time of discharge. Patients are classified into various categories based on most responsible diagnosis and other clinical features, to create groups of acute care inpatients that have similar clinical characteristics and resource utilization[51]. Costs are then assigned to groups based on relative resource use (see below). This information is housed in Discharge Abstract Databases (DAD) and is a source of costing data for inpatient admissions. Data from ambulatory services delivered by institutions, such as emergency department visits and day surgery, is also collected and classified using the National Ambulatory Care Reporting System (NACRS). Similar to the DAD, costs are assigned to the various groups based on relative resource utilization. Data from both of these sources provide patient level costing data for inpatient and ambulatory services provided by publicly run institutions[51].

Some health systems collect detailed itemized costing information specific to each inpatient encounter. These are called micro-costing databases and all direct and indirect costs incurred by each patient, detailed by individual services such as nursing, laboratories, diagnostic imaging, and pharmacy. These databases are both costly and labor intensive and are not broadly implemented in Canada and other publicly funded health systems[51]. The cost accounting approach used is determined by the purpose, with micro-costing offering the most detail.

2.2.2 Provincial Databases

Physician costs are not included in the institutional databases (DAD, NACRS and micro-costing databases)[51]. Physician claims data is available from the provincial ministries of health. These databases provide itemized claims for services, submitted by physicians for a specific patient. Each claim is associated with a fee based on the provincial schedule of medical benefits. Not all physicians are remunerated on a fee for service model and various other payment arrangements exist. These are broadly termed Alternative Relationship Plans (ARP). In most jurisdictions, physicians are required to submit claims for services to the health ministry to track clinical activities under these arrangements. These are referred to as shadow billings and can be used as a reasonable surrogate for physician costs[51].

Some outpatient pharmacy costs are covered by Provincial health care programs. The various medications that are covered and the patients that qualify, vary between Provinces. Individual patient dispensing information is available through Pharmacy Information Network (PIN) databases, and itemize the medication names and amounts dispensed[51]. Price lists are available by Province to allow a calculation of costs[54]. Pharmacy dispensing fees are standardized Provincially and must be added to each prescription[55]. The PIN data includes all prescribed medications. Any costs that are not covered, or only partially covered by the public payer are not reflected in this dataset.

2.3 Costing Methodologies

Costs can be measured using a top-down or bottom-up methodology. The bottom-up methodology is also referred to as micro-costing and involves accounting for all costs for services provided, both directly in the provision of care and the indirect costs that support the infrastructure required to provide it[51]. This methodology is rigorous and labour-intensive but provides specific costs for each patient being evaluated. There are many advantages to micro-costing but not every health system has the administrative infrastructure to provide that level

of data, nor is that level of detail usually needed. Top-down costing methodologies include simple per diem costs, a cost that is provided for a day in a given facility, regardless of location and diagnosis, as well as strategies based on Case Mix Groups. This methodology categorizes patients into groups of similar diagnoses with comparable resource use and costs[56]. Each are described in more detail below.

2.4 Top-down costing methodologies

2.4.1 Case Mix Costing

Case mix methodology is a top-down approach to health care costing. In the inpatient context, patients are classified into various categories based on diagnosis and other clinical features. This creates groups of patients that have similar clinical characteristics and resource utilization[51]. These were originally termed Diagnostic Related Groups (DRGs) that were developed by the US Medicare system[56]. DRGs are grouped by primary diagnosis using the International Classification of Diseases (ICD). In Canada, they were modified in 1983 by the Hospital Medical Records Institute (now called Canadian Institute for Health Information [CIHI]) as a Canadian version of their American counterpart[56].

CIHI receives discharge abstract data from institutions across the country submitted through the Canadian Management Information System Database (MIS). Using these data, CIHI has evolved DRGs into a classification system called Case Mix Groups + (CMG+). Rather than the primary diagnosis, patients are grouped based on the most responsible diagnosis; this is the diagnosis that is responsible for the greatest proportion of the hospital stay. The system also includes partitioning based on interventions using the Canadian Classification of Health Interventions (CCI) taxonomy. The CMG+ system is continuously evolving using a 3-year enhancement cycle[57]. For each group within the CMG+, a resource intensity weight it assigned. Resource Intensity Weight (RIW) is a measure of the average resource consumption during a hospital admission within a CMG+ grouping. A RIW of 1.0 equates to the resources consumed

during an average hospital stay. To capture resource use variability within CMG+ groups, CIHI uses age, level of comorbidity, and certain interventions associated with complexity and resource intensity, to further refine the RIW values. Expected Length of Stay (ELOS) are established for each CMG+ grouping and are used to identify long stay cases. RIWs are further adjusted for patients that have a length of stay that exceeds the ELOS for their CMG+ group. The RIWs and ELOS are updated yearly using 2 years of data[57].

Using this methodology, institutions classify their discharged patients into a given CMG+ grouping and assign a RIW to each patient. Given that the RIW represents the utilization for a standard hospital admission, the costs associated with a given patient's admission can be calculated by multiplying the RIW and the cost of an average hospital stay[57].

2.4.2 Cost of a Standard Hospital Stay (CSHS)

Along with clinical elements, CIHI also collects financial data from institutions through the Canadian Management Information System Database (CMDB). Most costs are included but some, such as amortization of buildings, land and equipment, termination benefits and compensation for medical personnel are not. Institutions also report cost by functional centre: nursing units, operating rooms, post anesthetic recovery rooms, emergency departments, ambulatory care, diagnostics and therapeutics, mental health and rehabilitation. For each functional centre, CIHI uses methodology to determine an allocation of costs to inpatient costs, outpatient costs, and non-patient costs. Using this approach, all costs associated with the care of inpatients for a given institution are determined[58]. CIHI then tallies an institution's total weighted cases using the RIW and total case mix for the year. An adjustment is made for patients with a length of stay greater than 365 days. In some jurisdictions, mental health and rehabilitation patients are reported separately and these patients are removed from the calculation accordingly. The cost of a standard hospital stay is then the total inpatient costs divided by the total weighted cases[58]. The CSHS is the full cost of treating an average acute care inpatient. CIHI reports the CSHS by institution and Province yearly[59].

2.4.3 Other approaches

There are other means of estimating inpatient costs that are less complex but less accurate. Per diem costs can be used and estimate costs by simply multiplying that cost by length of stay[51]. Average costs within a CMG are also available through CIHI's Patient Cost Estimator and segregated by Province and age group[60]. Alberta Health also provides costs by CMG using aggregated micro-costing data through its Interactive Health Data Application (IHDA)[61]. This provides cost estimates by CMG category region in Alberta and year.

2.5 Bottom up costing methodology: Micro-costing

Micro-costing is a technique that involves itemizing each element of utilization for a specific patient, assigning a cost to it, and aggregating them to provide a total cost. These are broken down to fixed and variable costs, or direct and indirect costs, including individual components such as labor, pharmaceuticals, general medical supplies, capital, and administrative costs, such as overhead[51, 62]. Depending on the perspective chosen, this might also include detailed assessment of out of pocket expenses, travel time, caregiver time, and lost wages[63].

Performing a micro-costing analysis on inpatient care requires detailed micro-costing databases. Patient-level data is available for physician services, using provincial physician claims data, and pharmaceuticals covered by provincial health systems.[51]. Other aspects of utilization, out of pocket and societal costs may be collected using activity logs, targeted questionnaires or direct observation[64].

Micro-costing is considered the gold standard given the patient specific detail it provides[51, 65]. It is of particular value when precise costs estimates across subgroups are needed as this is not as well captured in case mix techniques. This includes costing of new interventions within defined populations[64]. This methodology is needed to accurately capture all the facets of patient borne

costs, such as out of pocket expenses, when adopting the societal perspective[64]. The disadvantages of micro-costing are mainly related to time, complexity, and the cost involved in collecting the data[51]. While micro-costing provides a more precise reflection of the actual costs associated with the health care provided, it may be less reflective of typical cases that receive care[51]. It is a technique that will be more sensitive to outliers and generally provides higher costs when compared to other methods[65], regardless of the costing perspective used.

2.6 Measuring Health Care Costs

There is no one source data that provides a total cost for inpatient or outpatient care. Depending on the research question and context, multiple sources of costing data must be aggregated[51].

2.6.1 Inpatient costs

Inpatient costs can be calculated using the methodologies outlined above. Costs for physician services are not included in RIWs or micro-costing data and must be calculated separately[51]. It is important to note that top-down costing methodologies tend to produce lower cost estimates than micro-costing. One study, comparing micro-costing to DRG in Ireland, reported an underestimate of 66% for procedural care related to acute myocardial infarction and 50% for inpatient HIV care[66]. A study from Alberta demonstrated that for cardiac patients, CMG+ grouping methodology more closely reflected micro-costing compared to DRG; intraclass correlations of 0.86 for CMG+ compared to 0.76 for DRG[65]. While costing studies related to general ICU patients[67] and ARDS in particular[68], have used various methodologies, comparisons of one approach to the another in these populations are lacking.

2.6.2 Outpatient costs

Some health systems have micro-costing databases to track outpatient services, allowing less labour-intensive micro-costing techniques to be used[51]. Case mix costing techniques can also be applied to outpatients. The grouping system CIHI uses to classify outpatient visits is the Comprehensive Ambulatory Classification System (CACS)[51] and collects data using the National Ambulatory Care Reporting System (NACRS). This system gathers data on visits to emergency departments, diagnostic imaging, day surgery and other ambulatory interventions. RIWs have also been developed by CACS groupings to reflect resource utilization. The RIW is based on the CSHS and costs are estimated in the same way as inpatient costs[69].

2.6.3 Physician Claims

Costs related to physician claims are not included in the DAD or NACRS dataset[57]. Any costs associated with physician remuneration are removed from the calculation of the CSHS[58]. Many physicians are remunerated on a fee for service basis, through provincial fee schedules by submitted claims. Others have different financial arrangements that fall broadly under Alternative Relationship Plans (ARPs). Fee for service claims are available from provincial health ministries, are specific to the patient and physician, and provide direct costs associated with the services provided. In some Provinces, physicians that are compensated through ARPs are obliged to submit fee for service claims to the Province, a practice called shadow billing. Using the fees associated with shadow billing provides a reasonable surrogate for costs for physician services provided under these arrangements[51].

2.6.4 Outpatient Pharmaceutical Costs

In Alberta the publicly funded drug benefit program is run through Alberta Blue Cross[70] and pharmacies report dispensed prescriptions to the Provincial Information Network (PIN) Database[71]. This dataset provides patient-level data on the type of pharmaceutical and amount dispensed. The cost covered by government for each prescription is negotiated and published

in the Alberta Drug Benefit List (ADBL)[70] . A dispensing fee is also negotiated Provincially and covered by the Province through this program[55].

Chapter 3: **Research Objectives**

Objective 1:

We sought to summarize the current evidence on costs in ARDS by conducting a systematic review.

Objective 2:

We performed a costing analysis on a cohort of patients with ARDS in Calgary, Alberta to provide specific analyses in the Canadian context to permit comparisons against summative data to date. Our specific research questions were:

- What are the health care costs of an index admission for a patient with ARDS? What patient characteristics and clinical factors influence these costs?
- What are the 3-year health care costs for survivors of ARDS after discharge from the index admission? What patient and clinical factors influence these costs?

Chapter 4: Systematic Review of the Costing Literature in ARDS

Of note: This work was published in Chest in 2022:

Boucher PE, Taplin J, Clement F. The Cost of ARDS: A Systematic Review. *Chest*. 2022;161(3):684-696. doi:https://doi.org/10.1016/j.chest.2021.08.057

4.1 Introduction

The costing literature in ARDS has not been systematically reviewed and synthesized. Given the wide range of costs reported, a comprehensive review of the differences in populations studied, context, economic perspective, and methodology will be of value in understanding this variability. It will also provide an in-depth assessment of clinical factors that influence costs. This information will help inform the proposed costing analysis of our local ARDS cohort. Furthermore, a comprehensive synthesis of this literature will help contextualize the true cost of the syndrome and be of value to researchers and policy makers.

4.2 Study Design and Methods

The Cochrane methodology[72] was used to guide the review and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[73]. Using the population, intervention, comparator, outcomes and design framework (PICOD), a focus was made on adult patients with a diagnosis of ARDS. No comparator or specific intervention was required (Supplementary Table s1 for PRISMA checklist). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42020192487.

4.2.1 Search Strategy

Medline, Embase, Central and Econolit were used to search the literature for relevant articles through to April 29, 2021. The search strategy was based on the following components: Acute respiratory distress syndrome, acute lung injury, intensive care and cost. Each term was searched using subject specific terms and a series of keywords under each heading. Published filters were applied to limit the results to human studies, randomized control trials and cohort studies[74], without language or date restrictions (Supplementary Table s2). A hand search of the reference list of all articles identified for full text review was undertaken to find any studies not identified in the query. The citations were imported into citation management software (EndNote X9) and deduplicated.

4.2.2 Publication Review

The titles and abstracts were reviewed in duplicate. Studies to be considered for full text review reported cost data in a cohort of ICU patients with ARDS. The results of the scanning process were reviewed after the first 100 citations to ensure a consistent approach by both reviewers. Articles were considered for full text review if identified by at least one of the investigators. Full text review was undertaken in duplicate. Publications included in the systematic review were randomized control and observational trials that reported on cost data in an ARDS population. Agreement between reviewers for both steps was quantified using the kappa statistic and discrepancies were resolved by consensus.

4.2.3 Data Extraction

Data extraction from the publications kept for the systematic review was done in duplicate and included the type of study, patient characteristics, year, country, perspective, definition of ARDS, details of costing methodology, currency, currency year, costing time frame and costs. For economic evaluations of clinical trials, the costs for the control group were used unless

costs for the entire cohort were provided. If the currency was not adjusted to a common year, the last year of data collection was used. To compare costs to each other, all costs were converted to United States dollars (USD) using the average exchange rate of the currency year[75]. These costs were then inflated to 2021 USD using the Bank of Canada currency inflator[76]. Mean costs and standard deviations were compared across trials. If mean costs and standard deviations were not provided, they were estimated based on the median, interquartile range and number of patients using the method of Wan[77].

4.2.4 Quality Assessment

Study quality was assessed using a modified version of the Quality of Health Economic Studies (QHES) checklist. This 16-item checklist is a validated tool designed to measure the quality of health economic analyses[78]. As this systematic review was focused on costing studies rather than economic models, the QHES instrument was modified by removing the questions that pertain primarily to economic models and adding minor modifications to others. 7 questions were eliminated leaving a 9-item checklist (Supplementary Table s3). A graded approach was taken to assign a score to each item based on the quality and completeness of information in each publication allowing for partial marks. The weights from the original instrument were kept and the overall scores out of 59 were converted into a score out of 100 to provide an adjusted QHES score. Scores were assigned by each reviewer and differences were resolved by consensus. The quality of studies based on the adjusted score was then considered as previously described[79]: a score 75-100 was labeled “High quality”, 50-74 “Fair quality”, 25-49 “Poor quality” and 0-24 “Extremely poor quality”.

4.3 Results

The search strategy yielded 4663 records from the four databases with no additional studies identified through other sources. After deduplication, 4199 records were included in the title and abstract screen. 4047 were excluded with an additional 42 duplicates found, leaving 110

records for full text review. After full text review, 22 studies were kept for the systematic review. The kappa statistic for the full text review was 0.72 and 0.68 for the final inclusion, demonstrating "substantial" agreement between both reviewers[80]. The reasons for exclusion are detailed in the PRISMA flow diagram (Figure 1).

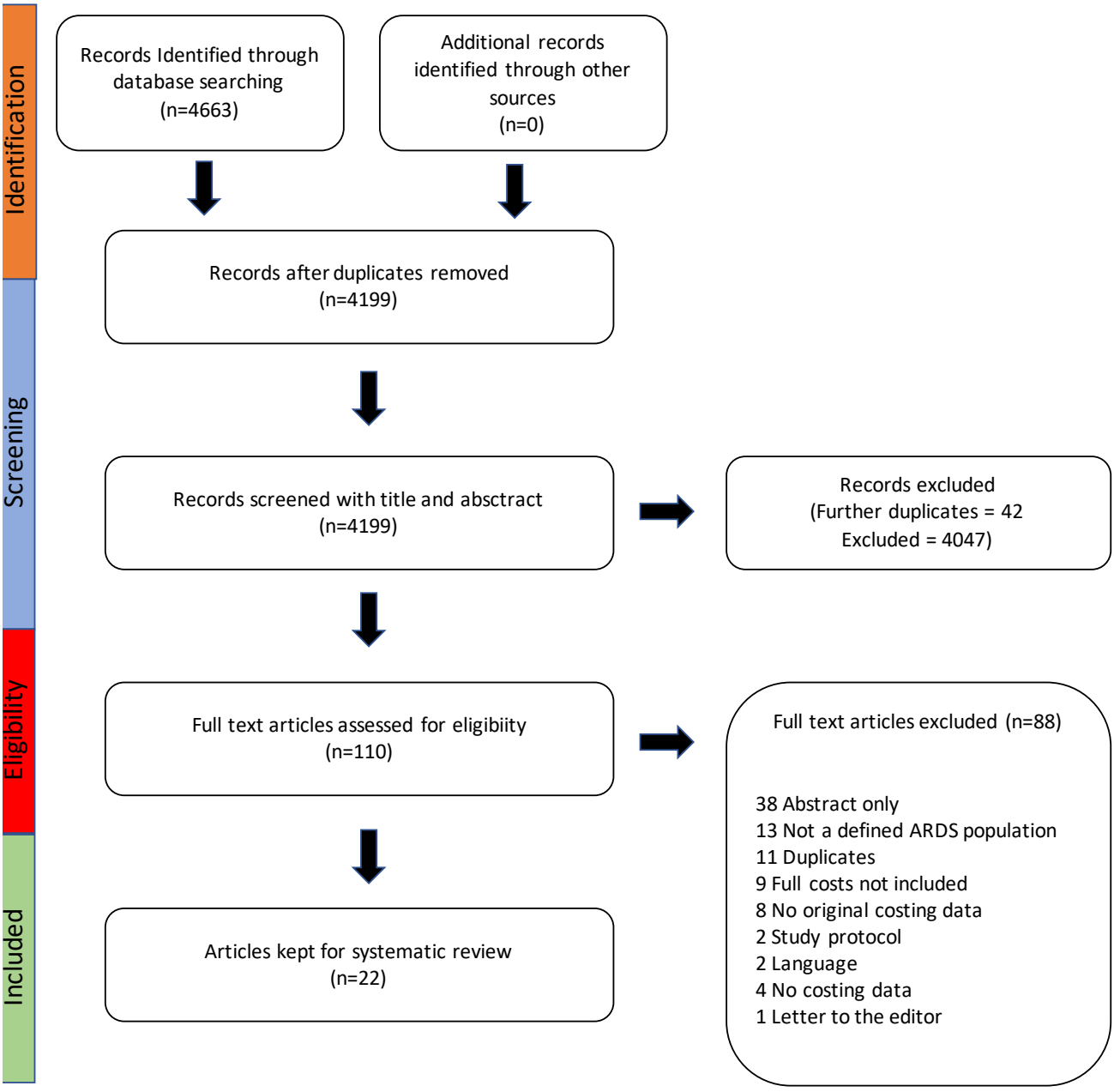

Figure 1: Flow Diagram for Identification of Abstracts and Final Eligibility (PRISMA Diagram)
ARDS: Acute Respiratory Distress Syndrome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

The 22 publications included cost analyses on a total of 49 483 patients with study publication dates between 1984 to 2021. Thirteen were from the United States[36, 38-40, 81-89], three from the United Kingdom[28, 37, 41], three from Canada[32, 43, 44], and one each from Taiwan[90], Brazil[91] and Finland[35]. Ten studies looked exclusively at the inpatient costs associated with the index ARDS admission[35, 36, 43, 82, 86-91]. Seven published the cost of the index ARDS admission along with post discharge costs for follow-up durations varying between 6 months and 2 years[28, 32, 37, 38, 41, 81, 85]. Three studies looked at post discharge costs only with a range of follow-up between 1 to 5 years[39, 40, 44]. Two studies looked at lost wages after surviving ARDS at 1 and 5 years[83, 84]. Characteristics of the studies are listed in Table 1. The majority of studies were prospective, used micro-costing techniques, and adopted the perspective of the institution, funded by either public health care or a third party (self-pay or private insurer)[See Table 2].

Author	Country	ARDS population	Definition of ARDS	Number of patients	Outpatient follow-up duration (If applicable)	Currency	Inpatient costs	Post discharge costs	Total costs**
Angus (2006)	US	Interventional study (iNO)	AECC (P/F≤250 mmHg)	312 (158 in control arm)	1 year	American dollars (2005)	$57,000 ($43,200) USD, Mean (SD)		
Bellamy (1984)	US	Cohort	Other	39	N/A	American dollars (1981*)	$52,894 ($9264-$187,955) USD, Median(range).		
Chen (2015)	Taiwan	Cohort	ICD-9	40,876	N/A	American dollars (2011*)	$6175.9 ($2279-$13,257) USD, Median (IQR)		
Cheung (2006)	Canada	Cohort (Toronto survivor cohort)	AECC (P/F ≤200 mmHg)	109	2 years	Canadian dollars (2002)	$128,860 ($111,970-$151,190) CAD, Mean, 95%CI	$28,350 ($20,580-38,350) CAD, Mean (95%CI)	
Clermont (2011)	US	Interventional Study (PAC)	AECC (P/F ≤300 mmHg)	655, (321 in control arm).	1 year	American dollars (2010)	$89,200 ($74,500) USD, Mean (SD)	$35,200 ($3,600) USD, Mean (SD)	$115,400 ($98,800) USD, Mean (SD)
Ferando (2021)	Canada	Cohort	Berlin	404 (152 in non-lung protective group, 252 in lung-protective group)	N/A	Canadian dollars (2018)	$58,993 ($40,382) CAD, Mean (SD) in non-lung protective group $48,292 ($38,378) CAD, Mean (SD)		
Herridge (2011)	Canada	Cohort (Toronto survivor cohort)	AECC (P/F ≤200 mmHg)	83	5 years	Canadian dollars (2009)		First year $22,309 , $9,885 at 2 years and $6063-$5566 CAD per year for years 3-5, Means (no SD provided).	
Kamdar (2017)	US	Cohort (ALTOS[A])	AECC (P/F≤300 mmHg)	67	1 year (lost wages)	American dollars (2017)			Lost wages at 1 year $26,949 ($22, 447) Mean (SD)
Kamdar (2018)	US	Cohort (ICAP[B])	AECC (P/F≤300 mmHg)	386	5 years (lost wages)	American dollars (2017			Lost wages at 5 years $180,221 ($110,285) Mean (SD)

Marti (2016)	UK	Interventional Study (HFOV[E])	AECC (P/F ≤200 mmHg)	795 or inpatient costing. 388 for post discharge data	1 year	British Pounds (2014)	£37,626 (£34,886-£40,385) GPB, Mean(95%CI)	£3935 (£2917-£4953) GBP, Mean (95%CI)	£44.077 (£41,168-46,985) GBP, Mean (95%CI)
McAuley (2018)	UK	Interventional study (simvastatin)	AECC (P/F≤300 mmHg)*	539 (280 in control arm)	1 year	British Pounds (2014)	£26,311 (£20,162) GPB, Mean (SD)		£29,171 (£24,171) GBP, Mean (SD)
Park (2014)	Brazil	Cohort	Berlin	Hypothetical model	N/A	Brazilian Real (2012*)	R$ 57,044 (R$ 1,868) BRL, Mean(SD)		
Peek (2009)	UK	Interventional Study (ECMO)	Murray score	180 (90 in control arm)	6 months	British Pounds (2005)			Mean £33,435 GBP (CI only reported for the difference)
Robles (2018)	US	Cohort (trauma)	Berlin	203	N/A	American dollars (2016*)	$450,888 ($224,901 - $827,529) USD, Median (IQR)		
Ruhl (2015)	US	Cohort (ICAP[B])	AECC (P/F≤300 mmHg)	138	2 years	American dollars (2013)	$138,005 ($98,822) USD, Mean (SD)	Inpatient only (re-admission) $54,629 ($71,156) USD, Mean (SD).	$182,182 ($174,200) USD, Mean (SD)
Ruhl (2017)	US	Cohort (ALTOS[A])	AECC (P/F≤300 mmHg)	764	1 year	American dollars (2014)		Inpatient (re-admission) $39,200 ($66,100) Mean (SD) Outpatient $6,671 (3,590-12,370) USD, Median (IQR)	
Ruhl (2017)	US	Cohort (ICAP[B])	AECC (P/F≤300)	123	5 years	American dollars (2014)		Inpatient (re-admission) $58,500 ($19,700-$157,800) USD, Median (IQR) Outpatient per year, range $4,918 ($4,192-$6,190) to $5,054	

								($4,291-$6,723) USD, Median (IQR)	
Salim (2006)	US	Cohort (trauma)	AECC (P/F ≤200 mmHg)	216	N/A	American dollars (2003*)	$267,037 ($256,548) USD, Mean (SD)		
Siddiqui (2019)	US	Cohort	ICD-9	3988	N/A	American dollars (2016)	$45,951.04 ($227) USD, Mean(SD)		
Treggiari (2004)	US	Cohort (trauma)	AECC (P/F≤300 mmHg)	205, 151 in ARDS cohort and 54 in ALI cohort	N/A	American dollars (2000)	$84,300 ($55,300-$127,200) USD, Median (IQR)		
Valta (1999)	Finland	Cohort	AECC (P/F ≤200 mmHg)	39	N/A	American dollars (1995*)	$43,000 ($5,500) USD, Mean(SD)		
Wiesen (2012)	US	Cohort	AECC (P/F≤300 mmHg)	45 (23 influenza and 22 non-influenza)	N/A	American dollars (2010*)	$342,000 ($203,000-$481,000), USD (flu), Mean(95% CI) $419,000 ($282,000-$556,000) (non-flu)USD, Mean(95% CI)		

Table 1: Clinical and cost details of publications

* Currency data not specified, last year of data collection used
** Total costs only from publications that specifically reported them
[A] ARDS Network Long-Term Outcomes Study (ALTOS)[92-95]
[B] Improving Care of Acute Lung Injury Patients (ICAP) study[96]

AECC: American European Consensus Conference
ALI: Acute Lung Injury
ARDS: Acute Respiratory Distress Syndrome
CAD: Canadian dollars
CI: Confidence Interval
ECMO: Extra corporal life support
GBP: Great Britain Pounds
HFOV: High frequency oscillation ventilation
ICD-9: International Classification of Diseases, 9th edition
iNO: Inhaled nitric oxide
IQR: Interquartile range
P/F: $Pa0_2/Fi0_2$ ratio
PAC : Pulmonary artery catheter
SD: Standard deviation
UK: United Kingdom
US: United States
USD: United States dollars

Author	Perspective	Costing methodology (inpatient)	Physician costs (inpatient)	Costing methodology (post discharge)	Physician costs (post discharge)
Angus (2006)	Institutional (Medicare/aid)	Prospective. Micro-costing, cost to charge	Included	N/A	N/A
Bellamy (1984)	Institutional (Third party payer)	Retrospective. Micro-costing. Charges.	No	N/A	N/A
Chen (2015)	Institutional (Public Health Care Payer: Taiwanese National Health Insurance Program)	Prospective. Not mentioned	Not mentioned	N/A	N/A
Cheung (2006)	Public Health Care Payer (OHIP)	Prospective. Micro-costing.	Included	Prospective. Mixed.	Included
Clermont (2011)	Societal (Medicare/aid + societal)	Prospective. Micro-costing. Cost to charge.	Included	Prospective. Micro-costing.	Included
Fernando (2021)	Public Health Care Payer (OHIP)	Prospective, Micro-costing	Not mentioned	N/A	N/A
Herridge (2011)	Public Health Care Payer (OHIP)	N/A	N/A	Prospective. Mixed	Included
Kamdar (2017)	Societal	N/A	N/A	Prospective. Questionnaire based. Theoretical calculation for lost wages.	N/A
Kamdar (2018)	Societal	N/A	N/A	Prospective. Questionnaire based. Theoretical calculation for lost wages.	N/A
Marti (2016)	Public Health Care Payer (NHS)/societal	Prospective. Micro-costing	Not mentioned	Retrospective. Mixed	Included
McAuley (2018)	Public Health Care Payer (NHS/Personal Social Service)	Prospective, micro-costing	Not mentioned	Prospective. Micro-costing.	Included
Park (2014)	Institutional (Public health care payer: Brazilian Unified Health System)	Model. Micro-costing.	No	N/A	N/A
Peek (2009)	Public Health Care Payer* (NHS)	Prospective, case mix	Included	Prospective. Micro-costing.	Included
Robles (2018)	Institutional (Third party payer)	Prospective, case mix (developed from their cohort). Charges	Not mentioned	N/A	N/A
Ruhl (2015)	Institutional (Medicare/aid)	Prospective. Micro-costing. Cost to charge.	Included	Prospective. DRG. Cost to charge.	Included
Ruhl (2017)	Institutional ("health care payer"/Medicare/aid)	N/A	N/A	Prospective. Mixed.	Included
Ruhl (2017)	Institutional (MEPS database)	N/A	N/A	Prospective. Mixed.	Not clear
Salim (2006)	Institutional (Third party payer)	Retrospective, micro-costing. Charges.	Not mentioned	N/A	N/A

Siddiqui (2019)	Institutional (Medicare/aid)	Prospective. Cost to charge, micro-costing	Not mentioned	N/A	N/A
Treggiari (2004)	Institutional (Medicare/aid)	Prospective. Micro-costing, cost to charge	Not mentioned.	N/A	N/A
Valta (1999)	Institutional (Public health care payer)	Prospective. Cost per TISS point.	Included	N/A	N/A
Wiesen (2012)	Iinstitutional (Third party payer)	Retrospective. Charges, micro-costing	Partial	N/A	N/A

Table 2 : Costing details from publications

* societal costs collected but not included in the analysis
OHIP: Ontario Health Insurance Plan
N/A: Not applicable
NHS: National Health Service
MEPS: Medical Expenditure Panel Survey
TISS: Therapeutic Intervention and Scoring System

The average adjusted QHES score for the 22 studies was 70, the highest score was 97 and the lowest 32 (Supplementary Table s4, Figure s1). The majority of studies were of high quality with thirteen achieving an adjusted QHES score of ≥75. Four were considered of fair quality with an adjusted QHES score of 50-74 and six were considered to be of poor quality with an adjusted QHES score of 25-49. No study scored in the extremely poor range. Higher quality studies had prospective data collection and tended to use micro-costing techniques. All economic evaluations carried out alongside a clinical interventional trial were rated as high quality.

The definition of ARDS varied, with most adopting variations of the American-European Consensus Conference criteria. Patient characteristics are listed in Table 1 and Supplementary Table s5. Seven publications were cost analyses associated with interventional clinical trials[28, 37, 38, 40, 41, 81, 83], and two reported costs at different time frames from the "ARDS Network Long-Term Outcomes Study" (ALTOS)[40, 83]; a prospective long term follow-up of 4 interventional trials[92-95] in ARDS. Three studies published costs for different time periods from the "Improving Care of Acute Lung Injury Patients (ICAP) Study cohort[39, 84, 85]; a prospective cohort of patients with ARDS from 11 ICUs in Baltimore, US[96]. Two studies reported on the costs at different time points in a cohort of ARDS survivors in Toronto, Canada[32, 44]. Three publications reported on the cost of ARDS in trauma cohorts[36, 86, 88]. Four studies reported on costs from ARDS cohorts, one from Finland[35], one from Canada[43], and two from the US[82, 89]. Two studies were retrospective

from administrative data sets, one from Thailand[90] and one from the US looking at the cost of ARDS in patients with gastrointestinal hemorrhages[87]. One study was an economic model[91] but was included as it used original cost data from an ARDS cohort in Brazil[97].

The majority of publications provided costs as means with standard deviations, others provided a median cost with interquartile ranges, and some provided both. All costs had large standard deviations and/or interquartile ranges reflecting the skewed nature of health care cost data. In order to compare costs across studies, median costs were converted to means using the method of Wan, converted to USD and inflated to 2021.

The highest mean cost reported for the index admission was $501,106 USD ($547,974 2021-USD) from an American study[36].The lowest mean cost was from Taiwan[90], $7,237 USD ($8,476 2021-USD) [Table 1, Figure 2, converted costs in Supplementary Table s6].

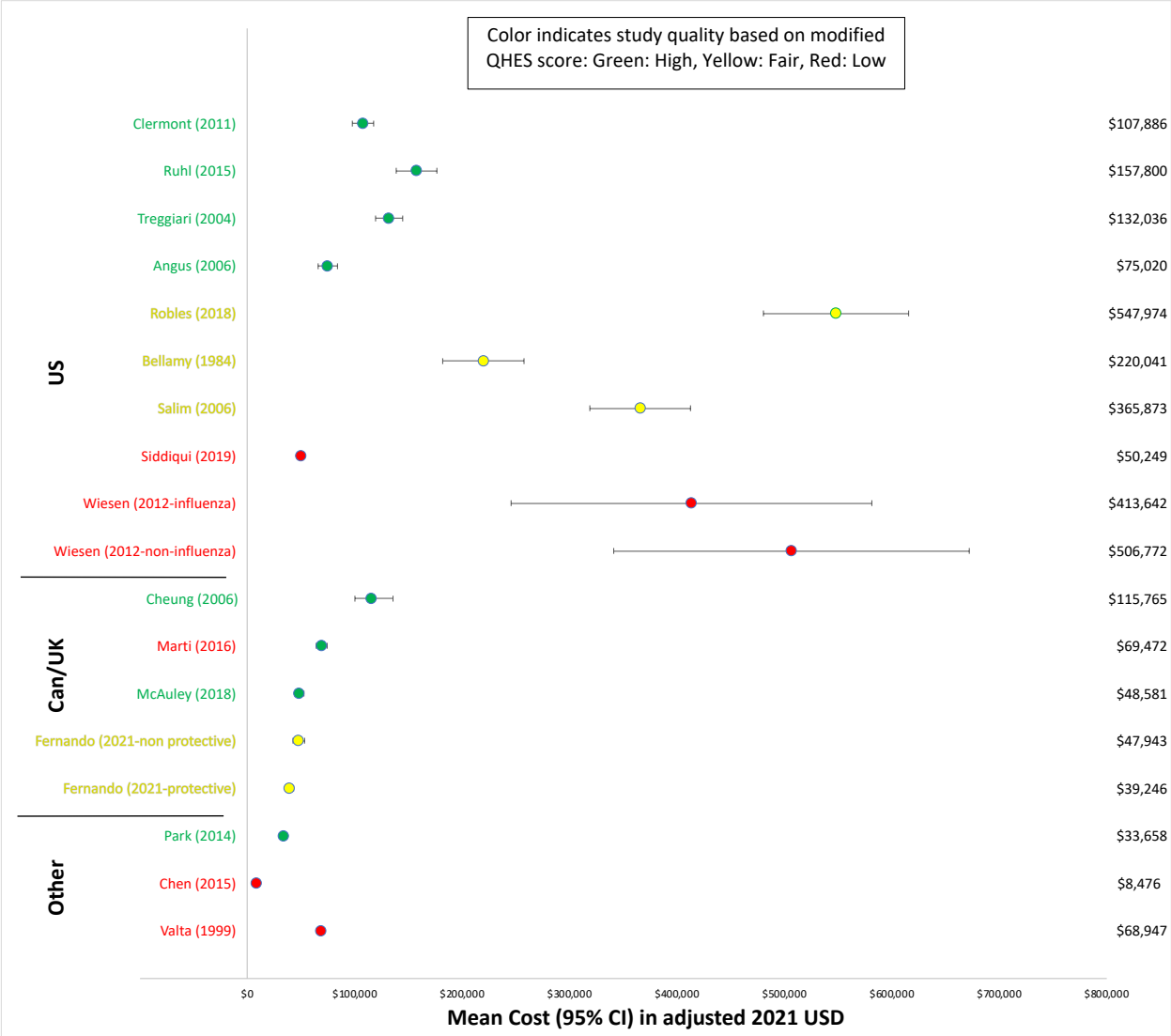

Figure 2: Forest plot, Inpatient Costs.

CI : Confidence Interval
QHES: Quality of Health Economic Studies
UK : United Kingdom
US : United States
USD : United States Dollars

Total mean costs at one year were as low as £29,171 GPB ($53,861 2021-USD) in a UK study[37] and as high as $115,400 USD ($139,574 2021-USD) in an American study[38]. Another American study reported mean total costs out to 2 years of $182,182 USD ($208,314 2021-USD)[85] (Table 1, Figure s2, converted costs in Supplementary Table s7). Isolated outpatient costs in the first year varied from a mean £3935 GBP ($7,266 2021-USD) from a study in the UK[41], to $35,200

USD ($42,574 2021-USD) from a study in the US[38] (Table 1, Figure s3, converted costs in Supplementary Table s8).

Lost wages were the focus of two publications from the US[83, 84] and they estimated the mean loss of income in survivors at 1 year to be $26,949 USD ($30,199 2021-USD) and at 5 years to be $180,221 USD ($193,903 2021-USD). One trial from the UK estimated that the loss of income for patients at one year varied from £2,994 GBP ($5,526 2021-USD) to £4,577 GBP ($8,451 2021-USD)[41]. Two trials collected costs from a societal perspective and included them in the total cost of care[38, 41]. One of these, a UK publication, provided both the cost using the societal perspective [£45,568 GBP ($82,896 2021-USD)] and the public health care payer perspective [£40,130 GBP ($73,003 2021-USD)][37]. Another UK study estimated societal costs but did not include these in their final result[28]. These costs varied from £2,212 GBP ($2,540 2021-USD) to £4,332 GBP ($4,974 2021-USD) over a 6-month period with the main driver being informal caregiver costs.

4.4 Discussion

22 publications were identified that reported on costs related to the care of patients with ARDS. This review demonstrates that there is variability in the way costs were calculated and reported. Most studies adopted the institutional perspective and the minority having a variable focus on societal costs. Most focused on the costs of the inpatient admission only and those that examined post discharge costs used different time frames. A limited range of health systems were reported with only 6 countries represented and the majority in America. This heterogeneity resulted in a wide range of costs, both between countries and within them, for the index admission and post discharge care. As a result, pooling results to provide a single cost was not felt to be reasonable.

The three publications with the highest costs for the index admission were all in American health care systems[36, 86, 89], and did not convert charges to cost using the centre-specific Centers for Medicare and Medicaid Services (CMS) conversion. Charges are the amounts that

appear on the patient's bill and do not accurately reflect the cost of care. In order to make comparisons across institutions it is best practice to convert charges to costs using the CMS charge to cost conversion[98]. None of these publications were judged to be of high quality based on the modified QHES score. Trauma also appeared to be a cost driver as two of these were from trauma cohorts[36, 86]. Increased post discharge costs were associated with duration of follow-up, rates of readmission and the American health care system[38, 39].

The societal perspective is generally associated with higher costs, but the studies that adopted this perspective did not demonstrate a significant increase. In these publications, one from the US and one from the UK, there was much higher overall third party health care costs relative to the societal ones[38, 41]. This lead to only relatively small increments from the addition of societal costs. However, lost wages have the potential to be an important component of societal costs. While these costs were included in both of these studies the methodology was different from the studies that focused on this question in isolation[83, 84], and substantially lower. If similar methodology had been used, these costs may have had an important impact upon the costs from the societal perspective.

The relationship between index admission costs and the severity of ARDS was variable. In one American trauma cohort there was an inverse relationship between cost and severity based on the Berlin definition[36]. Patients with mild ARDS had more costly admissions due to lower mortality and longer stays. This relationship was also seen in a UK study where overall costs were lower in the patients with lower P/F ratios owing to higher mortality and shorter lengths of stay[41]. In contrast, the opposite relationship was seen an American trauma cohort[88]. This may be related to an overall lower mortality in this cohort and a longer length of stay for patients with more severe disease. It was not possible to adequately compare costs and markers of severity of illness across studies due to variability in reporting them and lack of consistency in the type of severity score used (see Supplementary Table s9).

Most studies found that the overall costs during the index admission were lower for non-survivors due to shorter lengths of stay in those that died[28, 41, 86]. However, this relationship was not consistent with two studies, neither of high quality, reporting that non-survivors had higher inpatient costs[36, 82].

Understanding health care and societal costs related to ARDS is important for research into cost-effective interventions and for policy makers making decisions about resource allocation. The wide variation in reported costs reflect not only differences in patient population studied and costing methodologies, but also reflect the differences in costs of care in different health systems. The societal perspective is underrepresented in the literature and costs clearly extend beyond those to the health care system or third party/public payer.

Even though a pooled result could not be calculated, a range of costs based on the high quality studies by time frame and jurisdiction can be provided. These are presented in Table 3 and likely reflective of the true costs of care.

Country	Index admission cost (2021 USD)	Post discharge costs (2021 USD)	Total costs* (2021 USD)
US	$107,886[38] - $157,800[85]	$42,574[38] 1 year $62,465[85] 2 years	$139,574[38] 1 year $208,314[85] 2 years
Canada/ Europe	$39,246[43] - $115,765[32]	$7,266[41] 1 year $25,469[32] 2 year	$53,861[37]- $81,383[41] 1 year
Other	$8,476[90] - $68,947[35]	N/A	N/A

Table 3: Range of mean costs, based on high quality studies only by country (2021 USD)

* Total costs only from publications that specifically reported them
N/A: Not applicable
US: United States
USD: United States dollars

Inpatient costs may be higher for ARDS than other ICU syndromes such as sepsis; mean inpatient costs reported as $33,050 USD[99] ($37,791 2021 USD). Post discharge costs in the first year for ARDS patients may be more comparable to other conditions: $20,855 CDN ($19,329

2021 USD) in a sepsis cohort[100] and $31,412 CAD ($32,072 2021 USD) in a cohort with acute renal failure[101]. Awareness of these costs is more relevant than ever as patients with ARDS related to CoVID-19 have overwhelmed health systems in many parts of the world. Whether the health care and societal costs of ARDS secondary to CoVID-19 are comparable to other causes is not yet known as all cohorts in the publications preceded the pandemic.

There are a number of limitations in this review. We restricted our review to papers that looked at the costs in ARDS cohorts specifically and we may have missed publications with robust costing data in subgroups with ARDS within general ICU populations, or cohorts with mixed respiratory failure. Including publications on specific cohorts with ARDS, such as patients with trauma or upper gastrointestinal bleeding, might have biased costs towards other aspects of care. We chose to report on costs for the control arm in economic evaluations that were part of an interventional trial unless an aggregated total was provided. As a number of these interventions are part of current care pathways, the cost of some specific treatments, such as inhaled nitric oxide, pulmonary artery catheters and ECMO will be left out, potentially underestimating costs. Studies from lower and middle income studies were underrepresented in this review limiting applicability to those settings. We compared mean costs across studies as means are commonly used by policy makers when calculating total costs and are used in economic models[102]. Costing data in health care is positively skewed and median costs are therefore lower.

Quality assessment of costing studies is challenged by the lack of a quality assessment tool specific to this type of evaluation. Reporting standards such the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[103] statement was developed to help standardize the reporting of Economic Evaluations and not necessarily costing studies. The CHEERS statement was published in 2013 and predates a number of publications in this review. It was only mentioned specifically by three publications[39, 40, 85].We chose to evaluate the studies using a modified version of the QHES score. While there is not a specific quality tool to evaluate costing studies, these modifications have not been validated.

4.5 Interpretation

ARDS is a costly syndrome with significant resource utilization both during the index inpatient admission and in the years that follow. There is wide variation in costs reported owing to differences in populations studied, costing methodology and health system. There is a need for comprehensive costing data in this population to inform health care systems especially in light of the current pandemic related to Covid-19.

4.6 Chapter 4: Supplementary Appendix

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Sup Mat
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

Table s1: PRISMA Checklist (note: page numbers refer to the original publication).

Database:
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to April 28, 2021>

#	Query	Results from 29 Apr 2021
1	exp Acute Lung Injury/	6,775
2	exp Respiratory Distress Syndrome, Adult/	35,901
3	(ALI or ARDS).ti,ab.	20,419
4	(acute adj4 (lung injur* or distress syndrome)).mp.	30,487
5	((severe or hypoxic) adj4 (respiratory and failure)).mp.	7,554
6	or/1-5	66,073
7	limit 6 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")	17,835
8	limit 6 to "all adult (19 plus years)"	17,370
9	6 not 7	48,238
10	8 or 9	50,372
11	Economics/	27,319
12	exp "Costs and Cost Analysis"/	244,474
13	Economics, Nursing/	4,003
14	Economics, Medical/	9,131
15	Economics, Pharmaceutical/	2,982
16	exp Economics, Hospital/	25,067
17	Economics, Dental/	1,917
18	exp "Fees and Charges"/	30,659
19	exp Budgets/	13,816
20	budget*.ti,ab,kf.	31,274
21	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	241,919
22	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	312,755
23	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	174,235
24	(value adj2 (money or monetary)).ti,ab,kf.	2,567
25	exp models, economic/	15,580
26	economic model*.ab,kf.	3,523
27	markov chains/	14,917
28	markov.ti,ab,kf.	24,174
29	monte carlo method/	29,303
30	monte carlo.ti,ab,kf.	52,028
31	exp Decision Theory/	12,414
32	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	26,842
33	or/11-32	771,793
34	10 and 33	557

Table s2: Medline Search Strategy

Original QHES question	Modifications		Points (Total 59)
1. Was the study objective presented in a clear, specific, and measurable manner? (7 points)	None	Full marks if clear and specific.	7
2. Were the perspective of the analysis (societal, third-party payer, and so on) and reasons for its selection stated? (4 points)	None	Full marks if specifically mentioned and justified. No marks if implied but not stated.	4
3. Were variable estimates used in the analysis from the best available source (i.e., Randomized Control Trial-Best, Expert Opinion-Worst)? (8 points)	**Not used** as meant for economic models		
4. If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study? (1 point)	**Not used** as meant for economic models		
5. Was uncertainty handled by: (i) statistical analysis to address random events; (ii) sensitivity analysis to cover a range of assumptions? (9 points)	None	Full marks if sensitivity analysis (es) undertaken and probabilistic analysis	9
6. Was incremental analysis performed between alternatives for resources and costs? (6 points)	**Not used** as meant for cost effectiveness analyses and not primary costing articles.		
7. Was the methodology for data abstraction (including value health states and other benefits) stated? (5 points)	**Not used** as meant for economic models		
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3–5%) and justification given for the discount rate? (7 points)	**Not used** as meant for economic models not primarily costing studies.		

Original QHES question	Modifications		Points (Total 59)
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 points)	None	Full marks if comprehensive and micro-costed and CMS conversion of costs from charges.	8
10. Was the primary outcome measure(s) for the economic evaluation clearly stated and were the major short term, long term and negative outcomes included? (6 points)	None	Full marks if detailed account given and microcosting techniques used.	6
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 points).	**Not used**. Meant to evaluated health evaluation. Not part of all costing studies.		
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner? (8 points)	Kept but modified to assess methodology of cost analysis. "Were the choice of analytic methods comprehensive (ie strategies to deal with missing data, death, etc.)?"	Full marks if detailed, comprehensive and had a method to deal with missing data.	8
13. Were the choice of economic model, main assumptions and limitations of the study stated and justified? (7 points)	**Not used**. Meant for modeling studies.		
14. Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 points)	None	Full marks if discussed related to the economic endpoints not just clinical endpoints.	6
15. Were the conclusions/recommendations of the study justified and based on the study results? (8 points)	None		8
16. Was there a statement disclosing the source of funding for the study? (3 points)	None	Full marks if present somewhere in the publication.	3

Table s3: Modified QHES (Quality of Health Economic Studies) Checklist

Modified QHES question	1. Was the study objective presented in a clear, specific, and measurable manner?		2. Were the perspective of the analysis and reasons for its selection stated?		5. Was uncertainty handled by: (i) statistical analysis to address random events; (ii) sensitivity analysis to cover a range of assumptions?		9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?		10. Was the primary outcome measure(s) for the economic evaluation clearly stated and were the major short term, long term and negative outcomes included?		12.Were the choice of analytic methods comprehensive (ie strategies to deal with missing data, death, etc.)?		14. Did the author(s) explicitly discuss direction and magnitude of potential biases?		15. Were the conclusions/recommendations of the study justified and based on the study results?		16. Was there a statement disclosing the source of funding for the study?		Score	Adjusted score	Rating
Score		7		4		9		8		6		8		6		8		3	59	100	
Angus (2006)	Yes	7	No	0	No	0	Yes	8	Partly	4	Partly	6	Partly	4	Yes	8	Yes	3	39	66	**Fair**
Bellamy (1984)	Partly	4	No	0	No	0	Partly	4	Partly	3	Partly	4	Yes	4	Partly	4	Yes	3	28	47	**Poor**
Chen (2015)	Yes	7	No	0	No	0	Partly	2	Partly	3	Partly	4	Partly	3	Partly	4	Yes	3	26	44	**Poor**
Cheung (2006)	Yes	7	Partly	2	No	0	Yes	8	Yes	6	Yes	8	Partly	4	Yes	8	Yes	3	46	78	**High**
Clermont (2011)	Yes	7	Partly	2	Yes	9	Yes	8	Yes	6	Yes	7	No	3	Yes	8	Yes	3	53	90	**High**
Fernando (2021)	Yes	7	No	0	No	0	Partly	6	Yes	6	Partly	6	Partly	4	Yes	8	Yes	3	40	68	**Fair**
Herridge (2011)	Yes	7	Partly	2	No	0	Partly	6	Yes	6	Yes	8	Partly	4	Yes	8	Yes	3	44	75	**High**
Kamdar (2017)	Yes	7	Yes	4	Partly	5	Yes	8	Yes	6	Yes	7	Yes	6	Yes	8	Yes	3	54	92	**High**
Kamdar (2018)	Yes	7	Yes	4	Partly	5	Yes	8	Yes	6	Yes	7	Yes	6	Yes	8	Yes	3	54	92	**High**

Marti (2016)	Yes	7	Yes	4	No	0	Partly.	6	Yes	6	Yes	8	Yes	6	Partly	6	Yes	3	46	78	**High**
McAuley (2018)	Yes	7	Ye	4	Partly	5	Yes	8	Yes	6	Yes	8	Partly	3	Yes	8	Yes	3	52	88	**High**
Park (2014)	Yes	7	No	0	Yes	9	Partly	6	Yes	6	Partly	6	Yes	6	Yes	8	No	0	48	81	**High**
Peek (2009)	Yes	7	Yes	4	Yes	9	Partly	6	Yes	6	Yes	8	Yes	6	Yes	8	Yes	3	57	97	**High**
Robles (2018)	Yes	7	No	0	No	0	Partly	2	Partly	3	Yes	8	Partly	3	Yes	8	Yes	3	34	58	**Fair**
Ruhl (2015)	Yes	7	Partly	2	Yes	9	Partly	6	Yes	6	Yes	8	Yes	6	Yes	8	Yes	3	55	93	**High**
Ruhl (2017)	Yes	7	Partly	2	No	0	Partly	6	Yes	6	Partly	6	Yes	6	Partly	6	Yes	3	42	71	**Fair**
Ruhl (2017)	Yes	6	Partly	2	Partly	5	Partly	6	Yes	6	Yes	7	Yes	6	Yes	8	Yes	3	50	85	**High**
Salim (2006)	Partly	4	No	0	No	0	Partly	4	Partly	3	Partly	2	Partly	3	Partly	4	No	0	20	34	**Poor**
Siddiqui (2019)	Partly	4	No	0	No	0	Partly	4	Partly	3	Partly	4	Partly	2	Partly	2	No	0	19	32	**Poor**
Treggiari (2004)	Yes	7	Partly	2	Partly	5	Partly	6	Yes	6	Partly	4	Partly	3	Yes	8	Yes	3	44	75	**High**
Valta (1999)	Yes	7	No	0	No	0	Partly	6	Partly	3	Partly	4	Partly	2	Partly	4	No	3	26	44	**Poor**
Wiesen (2012)	Partly	4	No	0	No	0	Partly	4	Yes	6	Partly	4	Yes	6	Partly	4	No	0	28	47	**Poor**

Table s4: Modified QHES (Quality of Health Economic Studies) scores and overall rating of all publications

Author	Data collection	P/F Ratio Mean (SD) mmHg	Illness severity	Mortality	ICU LOS (days)	Ventilator Days (days)	Hospital LOS (days)
Angus (2006)	1996-1998 (plus one year follow-up)			28 day survival in the original cohort was 78%. Survival at one year for iNO 67.3% and 68.3% in the control group.	18.8 (13.9) [Mean (SD)] (all patients in the placebo group)		26.8 (23.4) [Mean (SD)] (all patients in the placebo group)
Bellamy (1984)	1979-1981			82%	10 (2-78) [Median (range)] for entire cohort.		33 (4-127) [Median(range)] for entire cohort.
Chen (2015)	1997-2011			57.8%			15 (6-30) [Median (IQR)]
Cheung (2006)	1998-2001 (2 year follow-up after)		APACHE II 23 (17-27) [Median (IQR)]	At 1 year 12 patients (out of 109) died. At 2 years another 8 died. A few were lost to follow-up at both follow-up time points.	25 (15-45) [Median (IQR)]	21 (12-40) [Median (IQR)]	48 (27-77) [Median (IQR)]
Clermont (2011)	200-2005 (plus one year follow-up)	127 (57)	APACHE III 93 (31) [Mean (SD)] For the cohort in the economic evaluation	Mortality 26.2% and 25.1% at 60 days for the PAC and control group respectively. At one year the mortality was 35.6% and 31.9%.			Post enrollment 23.8 (19.8) [Mean (SD)]
Fernando (2021)	2011-2017			39.4% in non-lung protective group. 32.5% in lung protective group	11 (7-17) days in non- lung protective group. 9 (5-15) in lung protective group [Median (IQR)]	8 (3-12) days in non-lung protective group 7 (2-10) days in lung protective group [Median (IQR)]	18 (6-35) days in non-lung protective group. 16 (5-33) days in lung protective group Median (IQR) .

Herridge (2011)	1998-2001 (5 year follow-up after)		APACHE II scores for those evaluated at 1 year 23 (17-27) and for those at 5 years 23 (16-28) [Median (IQR)]	At 1 year 12 patients died (8.3%). 9 more died in the following 4 years (19.2%)	For the cohort at 1 year 25 (14-47), and at 5 years 26 (16-49) [Median (IQR)]	1 year cohort 21 (12-40) and for the 5 year cohort 24 (12-41) [Median (IQR)]	The 1 year cohort 47 (26-73) and for the 5 year cohort 49 (29-72) [Median (IQR)]
Kamdar (2017)	2006-2014		APACHE II 23 (18-28) SOFA 5 (4-7) [Median (IQR)]	3 patients died during follow-up (4.5%)	14 (9-22) [Median (IQR)]	9 (5-14) [Median (IQR)]	23 (16-35) [Median (IQR)]
Kamdar (2018)	2004-2007	208 (80)	APACHE III 83 (26) [Mean (SD)]	7 patients (2%) died during follow-up	15 (12) [Mean (SD)]	11 (10) [Mean (SD)]	22 (16) [Mean (SD)]
Marti (2016)	2007-2012	113 (37.5)	APACHE II 21.8 (6.1) [Mean (SD)]	51.8% at 1 year. Reported for the original cohort even though this study is looking at survivors.	17 (16.5) [Mean (SD)]	HFOV 14.9 (13.3) and conventional 14.1 (13.4) [Mean (SD)]	33.6 (43.1) [Mean (SD)]
McAuley (2018)	2010-2014	132 (56)	APACHE II Simvistatin 19.4 (6.9) SOFA 8.6 (3.2), control 18.3 (6.2) SOFA 8.97 (2.9) [Mean (SD)]	28 day mortality. Simvistatin 22%, control 26.8%	Reported for survivors only. Simvistatin 13.9 (14.4) and control 14.4 (13.3) [Mean (SD)]	28 day ventilator free days, Simvistatin 12.6 (9.9), control 11.5 (10.4) [Mean (SD)]	Reported for survivors: Simvistatin 37.7 (64.5), control 35.4 (31.1) [Mean (SD)]
Park (2014)	2012	127 (57)					
Peek (2009)	2001-2006	75 (35.7)	APACHE II in ECMO group 19.68 (6.3) and in conventional group 19.9 (6.1) [Mean (SD)]	At 6 months, 50% mortality in conventional treatment arm and 36.7% in ECMO group.	ECMO 24 (13-50.4) conventional 13 (11-16) [Median (IQR)]		ECMO 35 (15.6-74) conventional 17 (4.8-45.3) [Median (IQR)]
Robles (2018)	2005-2016		No APACHE but Injury severity score 30(25-41) for patients with ARDS [Median (IQR)]	Overall mortality was 33% at 28 days and 36% at discharge. They also report mortality by severity.	14 (6-23) [Median (IQR)]	Vent free days reported 3 (0-17) [Median (IQR)]	18 (9-41) [Median (IQR)]
Ruhl (2015)	2006-2013		APACHE III 86 (26) [Mean (SD)]		14 (16) [Mean (SD)]		
Ruhl (2017)	2006-2013		APACHE II 23 (8) Daily SOFA 5 (2) [Mean (SD)]		19 (18) [Mean (SD)]		

Ruhl (2017)	2004-2012		APACHE II 23 (8) Daily SOFA 5 (2) [Mean (SD)]	45.4% (In-hospital) Follow-up period 3%.	19 (18) [Mean (SD)]		30 (22) [Mean (SD)]
Salim (2006)	2000-2003		ISS 26 (13) [Mean (SD)]	27.8% (In-hospital)	22.1 (21.1) {Mean (SD)]		32.2 (28.2) [Mean (SD)]
Siddiqui (2019)	2002-2012			ARDS with GIB 27% ARDS only 11%. (In-hospital mortality)			ARDS with GIB 11.93 (0.24) ARDS only 7.37 (0.03) [Mean (SD)]
Treggiari (2004)	1998		APACHE III for ARDS 70.8 (23.6) [Mean (SD)]	16% for ARDS (in-hospital)	ARDS 11 (81) [Median (Range)]		ARDS 22 (89) [Median (Range)]
Valta (1999)	1993-1995	114 (7)	Number of organ failures 2.6 (0.1) for survivors and 2.7 (0.2) for non-survivors [Mean (SD)]	ICU 37% In- hospital 42%.	23 (9-122) [Median (Range)]	20 (7-111) [Median (Range)]	46 (21-185) [Median (Range)]
Wiesen (2012)	2009-2010	P/F ratio (day 1), non-influenza 156 (95), influenza 150 (107)	Non-influenza APACHE III 89 (32) SOFA 9.2 (4.1), influenza APACHE III 66 (20) SOFA 8.3 (3.4) [Mean (SD)]	Non-influenza 77%, influenza 39%	Non-influenza 17 (25.5), influenza 12 (15) [Median (IQR)]		Non-influenza 24.5 (26.5), influenza 16 (22) [Median (IQR)]

Table s5: Patient characteristics from Publications

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
ECMO: Extra-corporeal Membrane Oxygenation
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
P/F: $Pa0_2/Fi0_2$ ratio
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

Author	Reported Costs (Inpatient)	Costs converted mean at 2021 USD Mean (95% CI)
Angus (2006)	$57,000 ($43,200) USD, Mean (SD)	$75,020 ($66,154-$83,886)
Bellamy (1984)	$52,894 ($9264-$187,955) USD, Median(range).	$220,041* ($182,091-$257,991)
Chen (2014)	$6176 ($2279-$13,257) USD, Median (IQR)	$8,476* ($8,383-$8,568)
Cheung (2006)	$128,860 ($111,970-$151,190) CAD, Mean(95%CI)	$115,766 ($100,592-$135,826)
Clermont (2011)	$89,200 ($74,500) USD, Mean (SD)	$107,886 ($98,028-$117,743)
Fernando (non-lung protective) (2021)	$58,993 ($40.382) CAD, Mean (SD)	$47,246 ($42,725-$53,160)
Fernando (lung protective) (2021)	$48,292 ($38,378) CAD, Mean (SD)	$39,246 ($25,395-$43,097)
Marti (2016)	£37,626 (£34,886-£40,385) GPB, Mean(95%CI)	$69,472($64,413-$74,566)
McAuley (2018)	£26,311 (£20,162) GPB, Mean (SD)	$48,581 ($44,220-$52,941)
Park (2014)	R$ 57,044 (R$ 1,868) BRL, Mean(SD)	$33,658 ($33,590-$33,726)
Robles (2018)	$450,888 ($224,901 - $827,529) USD, Median (IQR)	$547,974* ($480,288-$615,661)
Ruhl (2015)	$138,005 ($98,822) USD, Mean (SD)	$157,800 ($138,947-$176,654)
Salim (2006)	$267,037 ($256,548) USD, Mean (SD)	$365,873 ($318,996-$412,749)
Siddiqui (2019)	$45,951 ($227) USD, Mean(SD)	$50,249 ($50,241-$50,257)
Treggiari (2004)	$84,300 ($55,300-$127,200) USD, Median (IQR)	$132,036* ($119,291-$144,780)
Valta (1999)	$43,000 ($5,500) USD, Mean(SD)	$68,947 ($66,180-$71,715)
Wiesen (influenza) (2012)	$342,000 ($203,000-$481,000), USD, Mean(95% CI)	$413,642 ($245,524-$581,760)
Wiesen (non-influenza) (2012)	$419,000 ($282,000-$556,000) USD, Mean(95% CI)	$506,772 ($341,073-$672,471)

Table s6: Inpatient costs converted to means and 95% CI and inflated to 2021 USD.

*means and SD calculated from median, IQR or range using method of Wan[77]

BRL: Brazilian real

CAD: Canadian Dollars

CI: Confidence interval

GBP: Great British pounds

IQR: Interquartile Range

SD: Standard deviation

USD: United States dollars

Author	Reported Costs (Total inpatient and follow-up period)	Duration of follow-up	Costs converted mean at 2021 USD Mean (95% CI)
Clermont (2011)	$115,400 ($98,800) USD, Mean (SD)	1 year	$139,574 ($126,607- $152,541)
Marti (2016)	£44.077 (£41,168-46,985) GBP, Mean (95%CI)	1 year	$81,383 ($76,012-$86,752)
McAuley (2018)	£29,171 (£24,171) GBP, Mean (SD)	1 year	$53,861 ($48,634-$59,089)
Peek (2009)	Mean £33,435 GBP (CI only reported for the difference)	6 months	$80,053
Ruhl (2015)	$182,182 ($174,200) USD, Mean (SD)	2 years	$208,314 ($175,081-$241,548)

Table s7: Total costs of index admission and follow-up period, means and 95% CI and inflated to 2021 USD

CI: Confidence Interval
GBP: Great British Pounds
SD: Standard Deviation
USD: United States Dollars

Author	Reported Costs (Outpatient)	Duration of follow-up	Costs converted mean at 2021 USD Mean (95% CI)
Cheung (2006)	$28,350 ($20,580-$38,350) CAD, Mean (95%CI)	2 years	$25,469 ($18,489-$34,453)
Clermont (2011)	$35,200 ($3,600) USD, Mean (SD)	1 year	$42,574 ($42,097- $43,050)
Herridge (2011)	First year $22,309 , $9,885 at 2 years and $6063-$5566 CAD per year for years 3-5, Means (no SD provided).	5 years	$24,211 $10,728 $6,547 $6,041
Marti (2016)	£3935 (£2917-£4953) GBP, Mean (95%CI)	1 year	$7,266 ($5,386-$9,145)
Ruhl (2015)	Inpatient only (re-admission) $54,629 ($71,156) USD, Mean (SD).	2 years	$62,465 ($48,890-$76,040)
Ruhl (2017)	Inpatient (re-admission) $39,200 ($66,100) Mean (SD) Outpatient $6,671 ($3,590-$12,370) USD, Median (IQR)	1 year	$43,928 ($38,675-$49,180) $8,454 ($7,935-$8,972)*
Ruhl (2017)	Inpatient (re-admission) $58,500 ($19,700-$157,800) USD, Median (IQR) Outpatient per year, range $4,918 ($4,192-$6,190) to $5,054 ($4,291-$6,723) USD, Median (IQR)	5 years	$88,155 ($67,638-$108,671)* $5,715 ($5,418-$6,012)* $6,002 ($5,7641-$6,363)*

Table s8: Outpatient costs converted to means and 95% CI and inflated to 2021 USD.

*means and SD calculated from median, IQR or range using method of Wan[77]

CAD: Canadian Dollars
CI: Confidence Interval
GBP: Great British Pounds
IQR: Interquartile Range
SD: Standard deviation
USD: United States Dollars

Author	Country	P/F Ratio Mean (SD) mmHg	Illness severity	Mortality	Costs converted mean at 2021 USD Mean (95% CI)
Angus (2006)	US			28 day survival in the original cohort was 78%. Survival at one year for iNO 67.3% and 68.3% in the control group.	$75,020 ($66,154-$83,886)
Bellamy (1984)	US			82%	$220,041* ($182,091-$257,991)
Chen (2015)	Taiwan			57.8%	$8,476* ($8,383-$8,568)
Cheung (2006)	Canada		APACHE II 23 (17-27) [Median (IQR)]	Based on a cohort of survivors. At 1 year 12 patients (out of 109) died. At 2 years another 8 died. A few were lost to follow-up at both follow-up time points.	$115,766 ($100,592-$135,826)
Clermont (2011)	US	127 (57)	APACHE III 93 (31) [Mean (SD)] For the cohort in the economic evaluation	Mortality 26.2% and 25.1% at 60 days for the PAC and control group respectively. At one year the mortality was 35.6% and 31.9%.	$107,886 ($98,028-$117,743)
Fernando (2021)	Canada			39.4% in non- lung protective group. 32.5% in lung protective group	Non-lung protective: $47,246 ($42,725-$53,160) Lung protective: $39,246 ($25,395-$43,097)
Marti (2016)	UK	113 (37.5)	APACHE II 21.8 (6.1) [Mean (SD)]	51.8% at 1 year. Reported for the original cohort even though this study is looking at survivors.	$69,472($64,413-$74,566)
McAuley (2018)	UK	132 (56)	APACHE II Simvistatin 19.4 (6.9) SOFA 8.6 (3.2), control 18.3 (6.2) SOFA 8.97 (2.9) [Mean (SD)]	28 day mortality. Simvistatin 22%, control 26.8%	$48,581 ($44,220-$52,941)
Park (2014)	Brazil	127 (57)			$33,658 ($33,590-$33,726)
Robles (2018)	US		No APACHE but Injury severity score 30(25-41) for patients with ARDS [Median (IQR)]	Overall mortality was 33% at 28 days and 36% at discharge. They also report mortality by severity.	$547,974* ($480,288-$615,661)
Ruhl (2015)	US		APACHE III 86 (26) [Mean (SD)]		$157,800 ($138,947-$176,654)

Salim (2006)	US		ISS 26 (13) [Mean (SD)]	27.8% (In-hospital)	$365,873 ($318,996- $412,749)
Siddiqui (2019)	US			ARDS with GIB 27% ARDS only 11%. (In-hospital mortality)	$50,249 ($50,241- $50,257)
Treggiari (2004)	US		APACHE III for ARDS 70.8 (23.6) [Mean (SD)]	16% for ARDS (in-hospital)	$132,036* ($119,291- $144,780)
Valta (1999)	Finland	114 (7)	Number of organ failures 2.6 (0.1) for survivors and 2.7 (0.2) for non-survivors [Mean (SD)]	ICU 37% In- hospital 42%.	$68,947 ($66,180- $71,715)
Wiesen (2012)	US	P/F ratio (day 1), non-influenza 156 (95), influenza 150 (107)	Non-influenza APACHE III 89 (32) SOFA 9.2 (4.1) Influenza APACHE III 66 (20) SOFA 8.3 (3.4) [Mean (SD)]	Non-influenza 77% Influenza 39%	Influenza:$413,642 ($245,524- $581,760) Non-influenza: $506,772 ($341,073- $672,471)

Table s9: Inpatient costs and markers of severity.

*means and SD calculated from median, IQR or range using method of Wan[77]

APACHE: Acute Physiology and Chronic Health Evaluation

ARDS : Acute Respiratory Distress Syndrome

iNO: Inhaled Nitric Oxide

IQR: Interquartile Range

P/F: $Pa0_2/Fi0_2$ Ratio

SD: Standard Deviation

SOFA: Sequential Organ Failure Assessment

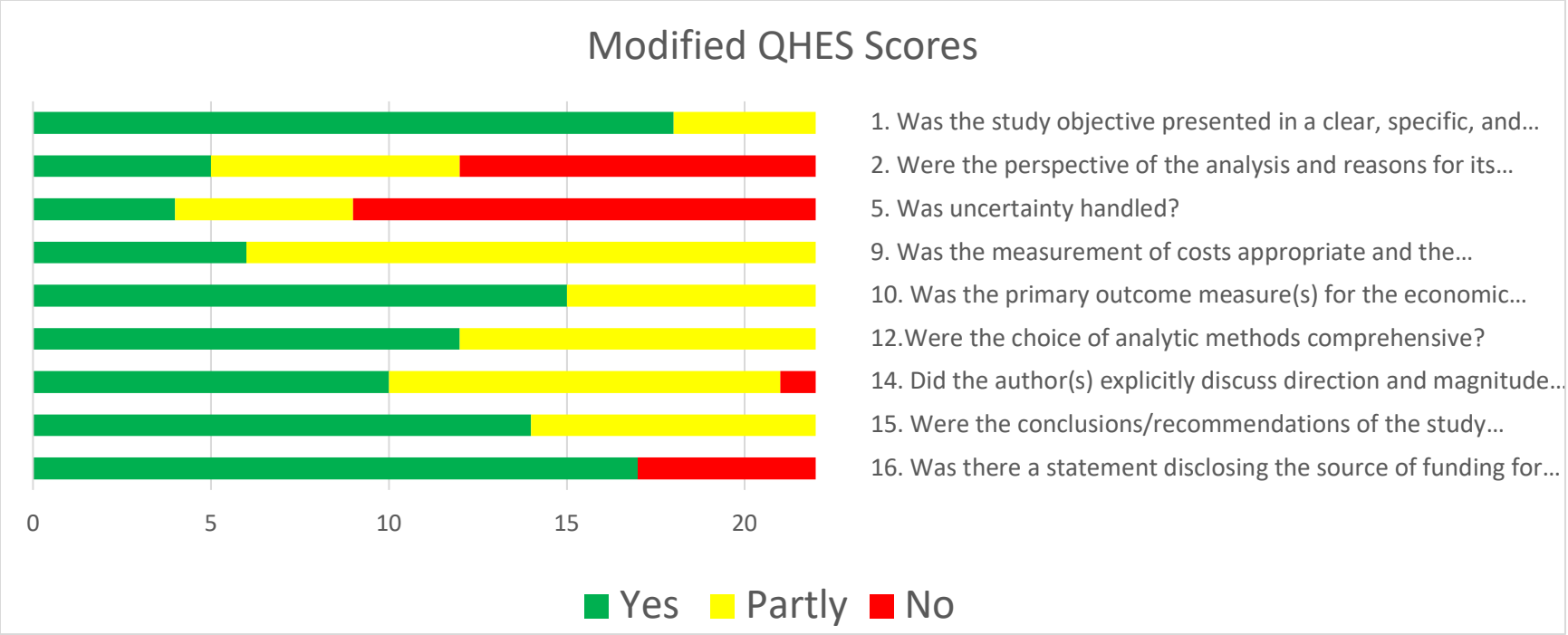

Figure s1: Distribution of Modified QHES (Quality of Health Economic Studies) Scores by question

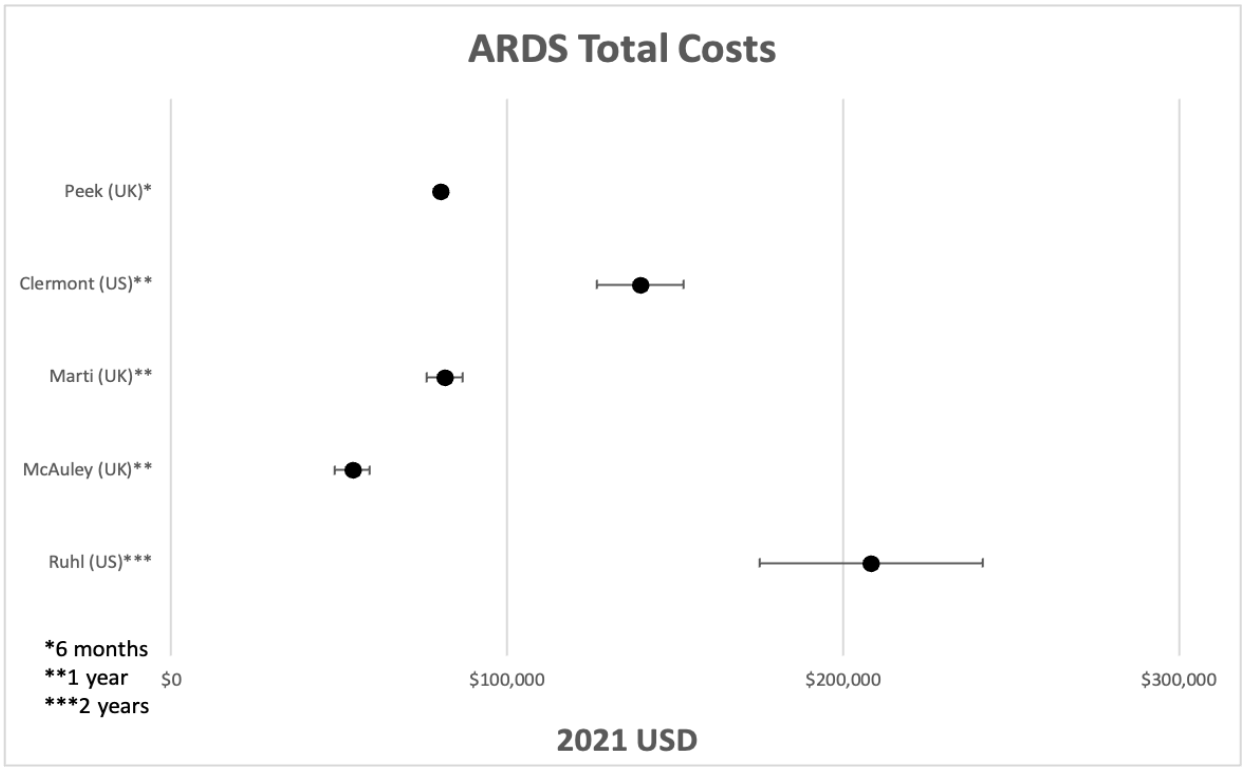

Figure s2: Forest plot of total costs

ARDS: Acute Respiratory Distress Syndrome

USD: United States Dollars

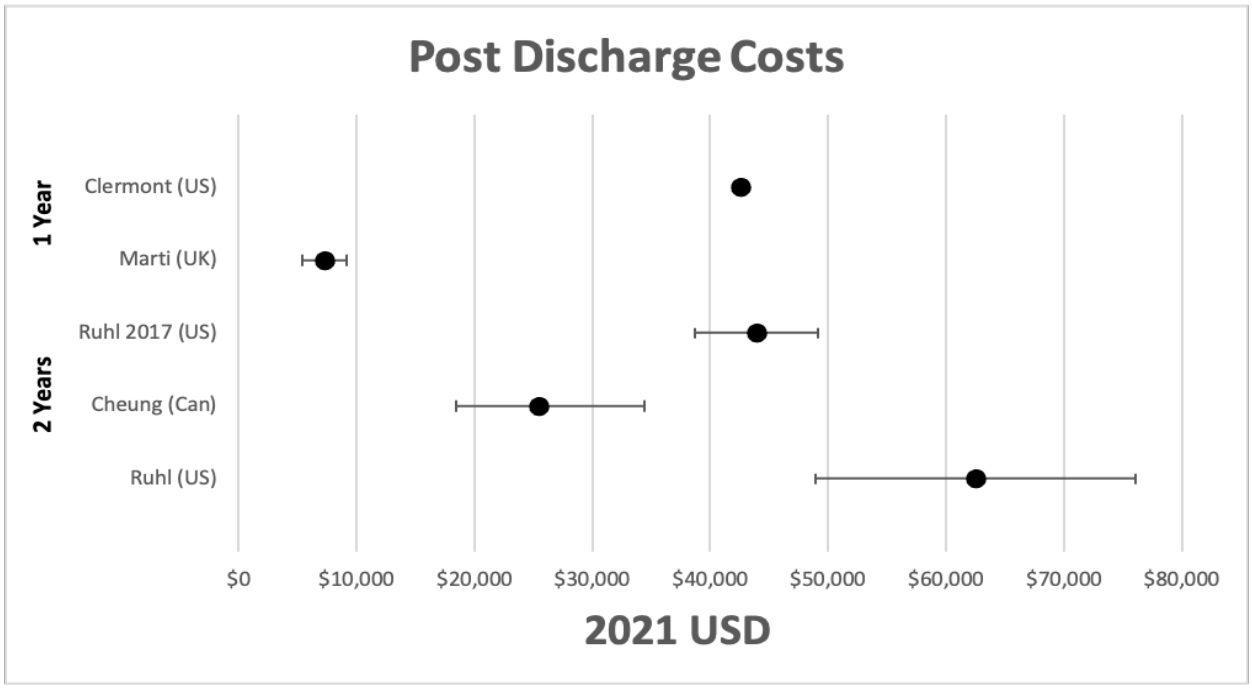

Figure s3: Forest plot of post discharge costs

USD: United States Dollars

Chapter 5 –Methods: Costing Study

5.1 Overview of Study design

A costing study of a prospective cohort of patients with sustained ARDS from the perspective of the publicly funded health care system was completed. This included both the costs for the index inpatient admission as well as a follow-up period of 36 months following discharge.

5.2 The Clinical Cohort

The patient cohort was part of a prospective observational cohort study[12]. It was a quality improvement initiative conducted in all 4 adult ICUs in Calgary, Alberta, designed to standardize the identification of patients with ARDS. Patients were consecutively enrolled between October 2010 and December 2012, if they were admitted to the ICU, invasively ventilated for more than 24 hours, and had a P/F ratio of $\leq$ 300 mmHg. They were then screened with an ABG on standardized ventilatory settings with an Fi02 of 1.0 for 30 minutes. Chest X-rays and the Berlin criteria for ARDS were adjudicated by two independent reviewers retrospectively. Patients were considered to have sustained ARDS if they continued to meet Berlin oxygenation criteria on a second standardized AGB criteria 12-48 hours after the initial diagnosis. The severity category was based on the second ABG.

Clinical data validated by nursing and respiratory therapists, and outcomes were collected prospectively using the electronic clinical information systems as well as manual chart extraction[12]. Post discharge mortality was obtained though data linkage with Alberta Vital Statistics to capture a full 36 months post discharge. At the end of the follow-up period, patients' postal codes and Personal Health Numbers (PHN) were checked to ensure that they had a valid Alberta postal code at the time of their last entry into the Discharge Abstract Database (DAD) or National Ambulatory Care Reporting System (NACRS) database. Costs were obtained through linkages with the DAD, NACRS, physician claims, and Pharmaceutical

Information Network (PIN) databases. Alberta Health Services does have a micro-costing database but due to a gap in its use in 2012/13 that coincided with this study, this information could not be used.

5.3 The inpatient and outpatient cohorts

The inpatient cohort was made up of patients with sustained ARDS that had an Alberta PHN, an Alberta Postal code at the time of the index admission, and linkage to the costing databases. The post discharge cohort consisted of the survivors to discharge from the inpatient cohort.

All patients in the inpatient cohort were assumed to have complete costs. Patients that died during the index admission period were also considered to have complete costs. Given that Alberta has one provincial health care delivery system, all publicly funded health care expenses provided in the Province are reflected in the provincial costing databases. As such, patients who were part of the post discharge cohort that had a valid PHN and Alberta postal code at end of the follow-up period, were considered to have complete costs. Patients that died during the follow-up period and had a valid PHN and Alberta postal code when checked at the end of the follow-up period were also considered to have complete costs. Patients that no longer had a valid Alberta postal code during the follow up period may have received health care services outside of the Province. As there were no means of accounting for these costs, we excluded these patients from the post discharge analysis.

5.4 The index admission

The index admission was defined as the admission during which the diagnosis of ARDS was made. The index admission included time spent at a different acute care facility, before and after the ICU admission when the diagnosis of ARDS was made. To capture any costs related to an emergency department (ED) visit associated with the admission, NACRS and physician claims data the day prior to the index admission were included. Alternative level of care (ALC) days are

captured in the DAD[59] but costs related to discharge to a non-acute care facility were not captured.

5.5 Costing Databases and cost calculation for the index admission

Costs were calculated using the Resource Intensity Weight (RIW) from the DAD. The RIW was multiplied by the Cost of a Standard Hospital Stay (CSHS) for the year associated with the discharge date from the index admission. The CSHS was obtained from the Canadian Institute for Health Information (CIHI)[104]. If the patient was transferred between acute care sites in the Province during the index admission, the cost of each hospital stay was summed. Costs during the index admission from the NACRS database were also included using the RIW and the CSHS from the year of discharge. In addition, to capture ED costs associated with the index admission, any NARCS visit from one day prior to the index admission was also included. Physician claims from one calendar day prior to admission until the discharge date were included in the index admission costs. Shadow billings were used for any physician billing through an alternative relationship plan (ARP).

The cost calculation for the index admission was the sum of the DAD RIW costs for the entire index admission, the NACRS RIW costs and physician claims. All costs were indexed to 2016 CAD using the Bank of Canada currency inflator[76]. The discharge year of the index admission was used as the base year to be from which to be indexed.

5.6 Costing Databases and cost calculation for the post discharge period

The post discharge follow-up period was for 36 months following the discharge date of survivors from the index admission. While all patients were identified prospectively, they were not formally followed. Administrative data was used to follow their publicly funded health care utilization and costs. Patients that no longer had a valid Alberta postal code during the follow up period were excluded from the post discharge analysis. The DAD was used to identify re-

admissions to hospital and costs were calculated using RIW and the CSHS for the year of discharge from that admission. Re-admissions that began prior to the end of the follow-up period were included, even if the discharge date was after the follow-up period. All ambulatory costs were captured using the NACRS database, the associated RIW and the CSHS for the year the service occurred. Physician claims were captured using the physician claims database. Shadow billings were used for those physicians on an ARP. Pharmaceutical costs were captured using the PIN database and calculated using the Alberta Blue Cross Drug Benefit List prices[54]. The list from 2016 was no longer available and prices from 2022 were used, assuming only nominal change in the price of most pharmaceuticals over this period. The provincially negotiated dispensing fee of $12.15 was added to all prescriptions[55]. The cost calculation for the post discharge period was the sum of the DAD RIW costs, the NACRS RIW costs, total of physician claims and costs related to PIN entries. The DAD, NACRS and physician claim costs were inflated to 2016 CAD based on the last year of follow-up or death, using the Bank of Canada cost inflator.[76] Given that the PIN costs and dispensing fee are 2022 prices, they were deflated to 2016 CAD using the same technique.

5.7 Analytic considerations with health care costs

Health care costs do not generally follow a normal distribution and are commonly positively skewed. While it is reasonable to discuss median and interquartile ranges for non-parametric data, including means and standard deviations for costs is also of value[105]. The mean costs is a better reflection of the actual costs for the population which is important for decision makers and economic modeling[52, 105].

Regression analyses of health costs can present challenges. When costs are used as the dependent variable in a regression model, a non-normal distribution can lead to issues with fit and stability. Costs are frequently transformed to improve regression models but make the results more challenging to interpret. Threshold models that use percentile cost cut offs and logistic regression may have a role in some situations[106].

Outpatient costs have additional considerations. Along with skewed distributions, there may be large number of patients with no costs, and patients that are lost during the follow-up period. If the number of patients with no costs is substantial, some have used two-step models to isolate the characteristics that are associated with incurring costs and characteristics that are associated with costs incurred[106]. If large number of patients are lost during the follow-up period, survival models have been used to account for this type of censorship[106].

5.8 Analysis

All statistics were performed on Stata 15. Continuous clinical variables that were normally distributed were presented as means with standard deviations and tests of hypothesis was the Student's t test. Continuous variables that were skewed were presented as medians with interquartile ranges and tests of hypothesis was Wilcoxon rank sum or Kruskal Wallis as appropriate. Categorical variables were presented as proportions and tests of hypothesis used the Chi^2 test.

5.8.1 Index admission costs

Total costs for the index admission cost and the contribution from each of the costing databases (DAD, NACRS and physician claims) were calculated for the entire cohort. A subgroup analysis was undertaken comparing total index admission costs by severity, sex, and vital status at discharge. The contribution from each of the databases was also calculated for these subgroups.

To assess what clinical factors influence total inpatient admission costs a multivariate regression analysis was undertaken. The approach was a backwards selection methodology[107], removing variables that did not reach statistical significance until the remaining were statistically significant ($p<0.05$). The dependent variable was total inpatient costs. The

candidate independent variables are provided in Table 1. The model was assessed for fit by using the R^2 value and examination of the residuals. The following planned substitutions for independent variables were assessed in an attempt to improve the fit of the model:

- Age as a continuous variable
- BMI as a continuous variable
- P/F as a continuous variable for ARDS severity
- Consideration of interaction terms

Patient Demographics	Variable Type	
Age ≥ 65	Binomial	Higher mortality with increasing age[108, 109]. Age over 65 associated with worse outcomes[9].
Female sex	Binomial	Worse outcomes for females[110]
BMI ≥ 30 kg/m^2	Binomial	Lower mortality[111]
Vital status at discharge from the index admission (Alive/Deceased)	Binomial	Associated with costs (lower[28, 39, 41] or higher[36, 82])
Severity of Illness		
ARDS severity (mild, moderate, severe)	Categorical	Higher mortality[11, 109], associated with costs (lower[36, 41] or higher[88])
Modified SOFA score at admission	Continuous	Higher mortality[109]
ARDS Risk factors		
- Primary pulmonary diagnosis: combination of o Pneumonia o Aspiration o Inhalation injury o contusion o pulmonary vasculitis o drowning	Binomial	Primary pulmonary causes of ARDS may have worse outcomes[112]
- Sepsis	Binomial	Higher mortality[13]
- Major Trauma	Binomial	Lower mortality[113], higher costs[68]
- Surgery	Binomial	Worse outcome in surgical patients[114]
- Pancreatitis	Binomial	Worse outcomes in pancreatitis[115]
Comorbidities		
≥ 2 of the following comorbidities: - Stroke - COPD - CAD - Heart Failure - Chronic renal failure - Chemotherapy - Hematological Malignancy - Metastatic cancer	Binomial	Increased comorbidities associated with worse outcomes[9, 109].

- Peripheral vascular disease - Chronic liver disease - Diabetes - Quadriparesis - Alcohol abuse - Organ insufficiency		
Specific Comorbidities - Malignancy - Alcohol use - Chronic liver disease	Binomial	Have been associated with a worse outcome Independently[13, 109]

Table 1: Candidate independent variables for the multivariate regression model for total index admission costs.

ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
CAD: Coronary Artery Disease
COPD: Chronic Obstructive Lung Disease
SOFA: Sequential Organ Failure Assessment

Further manipulations were attempted to improve the fit of the model: truncation of cost outliers (below the 5th percentile and above the 95th percentile) and log transformation of total index admission costs (natural log).

5.8.1.1 Justification for choice of independent variables in the multivariate regression model for total index admission costs

Patient factors that are associated with costs in ARDS include severity[36, 41, 88] and major Trauma[68]. Severity has been shown to be associated both with higher[88] and lower costs[36, 41]. Trauma may be associated with higher index admission costs[68]. Mortality is associated with both lower[28, 39, 41] and higher[36, 82] costs.

Given that the published literature on factors that are associated with costs in ARDS is limited, variables associated with outcome were chosen as surrogates. In ARDS, the following variables have been shown to be related to worse outcomes. Demographic factors: increased age[9, 108, 109] and female sex[110]. Underlying conditions: sepsis[116], active neoplasm[109], immunosuppression[109], hematologic neoplasm[109], chronic liver failure[109], alcohol use[117]. Severity of illness: oxygenation status (Berlin criteria[11], P/F ratio[109]), severity of illness scores (non-pulmonary SOFA[109], APACHE

II[108]). Increased Body Mass Index (BMI) and ARDS in patients with major trauma may be associated with a lower mortality[111 113]. Worse outcomes have been found in pancreatitis[115] and in surgical patients[114]. Primary pulmonary causes of ARDS may have worse outcomes than non-pulmonary causes[112].

5.8.2 Post discharge costs

Patients that did not have a valid postal code at the end of the follow-up period were removed from this analysis. For the remaining cohort, total post discharge and the contribution from each of the costing databases (DAD, NACRS, physician claims and PIN) were calculated for the entire cohort. A subgroup analysis was undertaken comparing total post discharge costs by severity of ARDS during the index admission, sex, and vital status at the end of the follow-up period. The contribution from each of the databases was calculated for these subgroups. The cost per event was calculated (cost per re-admission, NARCS encounter, general practitioner and specialist claim, and prescription).

To assess what clinical factors influence total post discharge costs, a multivariate regression analysis was undertaken. The approach was a backwards selection methodology[107], removing variables that did not reach statistical significance until the remaining were statistically significant ($p<0.05$). The dependent variable was total post discharge cost. The candidate independent variables are provided in Table 2. The model was assessed for fit by using the R^2 value and examination of the residuals. The following substitutions for independent variables were assessed in an attempt to improve the fit of the model:

- Age as a continuous variable
- BMI as a continuous variable
- P/F as a continuous variable for ARDS severity

Patient Demographics	Variable Type	
Age≥ 65	Binomial	Higher mortality with increasing age[108, 109]. Age over 65 associated with worse outcomes[9].
Female sex	Binomial	Better functional outcomes post discharge[118]
BMI ≥ 30 kg/m^2	Binomial	Higher post discharge needs[119]
Vital status at the end of the follow-up period (Alive/Deceased)	Binomial	
Severity of Illness during the index admission		
ARDS severity (mild, moderate, severe)	Categorical	Not independently associated with post discharge costs or mortality[22]
Other markers of severity during the index admission		
Hospital length of stay	Continuous	Increased risk of readmission[120]
ICU length of stay ≥ 10 days	Binomial	Poor long-term outcomes[121]
Ventilator days	Continuous	Increased duration associated with mortality[122]
ARDS Risk factors		
- Sepsis	Binomial	Increased cost and health utilization post discharge[123]
- Major Trauma	Binomial	May be associated with better post discharge outcomes[22]
- Surgery	Binomial	Higher risk of re-admission with any post-operative complication[124]
Comorbidities		
≥ 2 of the following comorbidities: - Stroke - COPD - CAD - Heart Failure - Chronic renal failure - Chemotherapy - Hematological Malignancy - Metastatic cancer - Peripheral vascular disease - Chronic liver disease - Diabetes - Quadriparesis - Alcohol abuse - Organ insufficiency	Binomial	Increased comorbidities associated with worse outcomes[44].

Table 2: Candidate independent variables for the multivariate regression model for total post discharge costs.

ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
CAD: Coronary Artery Disease
COPD: Chronic Obstructive Lung Disease
ICU: Intensive Care Unit

Further manipulations were attempted to improve the fit of the model: truncation of cost outliers (below the 5th percentile and above the 95th percentile) and log transformation of total post discharge costs (natural log).

5.8.2.1 Justification for choice of independent variables in the multivariate regression model for total index admission costs

Post discharge costs have been shown to be associated with the number of coexisting illnesses at the time of ICU admission (≤1 vs. ≥2 coexisting illnesses)[44]. Patients with sepsis have also been found to have increased cost and health utilization post discharge[123].

Given that the published literature on factors that are associated with post discharge costs in ARDS is limited, variables related to outcome were chosen as surrogates. ICU length of stay beyond 10 days has been shown to correlate with poor long-term outcomes[121]. Duration of hospitalization is associated with an increased risk of readmission[120] and with 1-year mortality in ARDS survivors[22]. Age and comorbidities are corelated with increased mortality at 1-year in ARDS survivors[22]. Obese patients may have higher post discharge needs after an admission for ARDS[119]. Longer durations of mechanical ventilation may be associated with increased mortality at 1 and 5 years[122]. Females may have better functional outcomes after hospital admission for ARDS[118]. Surgical patients that suffer post-operative complications are at higher risk of re-admission[124]. ARDS associated with trauma may have better post discharge outcomes[22]. Mortality during the post discharge period will have an influence on costs depending on the timing of the event, if it occurred in hospital and the duration of follow-up.

Severity of illness markers are not independently associated with mortality at one year[22], but ARDS severity during the index admission was included in the model nonetheless to assess the relationship between severity and post discharge costs.

Chapter 6: Results

6.1 Cohort description

The cohort of patients used in this study were drawn from a prospective observational trial, in which 7944 patients were screened for ARDS between October 2010 and December 2012, across the 4 adult ICUs in Calgary, Alberta, Canada[12]. 1250 of these patients were invasively mechanically ventilated for greater than 24 hours, with a P/F ratio of $\leq$ 300 mmHg on a standardized ABG. 731 met Berlin criteria for ARDS with 633 of these patients classified as having sustained ARDS by maintaining a P/F ratio $\leq$ 300 mmHg on a follow-up ABG 12-36 hours later. 585 of these patients had a link to the Alberta Health Services (AHS) Discharge Abstract Database (DAD) and a valid Alberta PHN. This group made up the economic cohort for this study and all were considered to have complete costs. 374 of these patients survived to discharge (36% mortality) and made up the post discharge economic cohort. There were 10 patients that no longer had an Alberta Postal Code when the DAD and NACRS databases were queried in May of 2017. These 10 patients were removed from the post discharge costing analysis. The remaining 364 in the post discharge cohort were considered to have complete costs. The flowsheet describing patient details is presented in Figure 1.

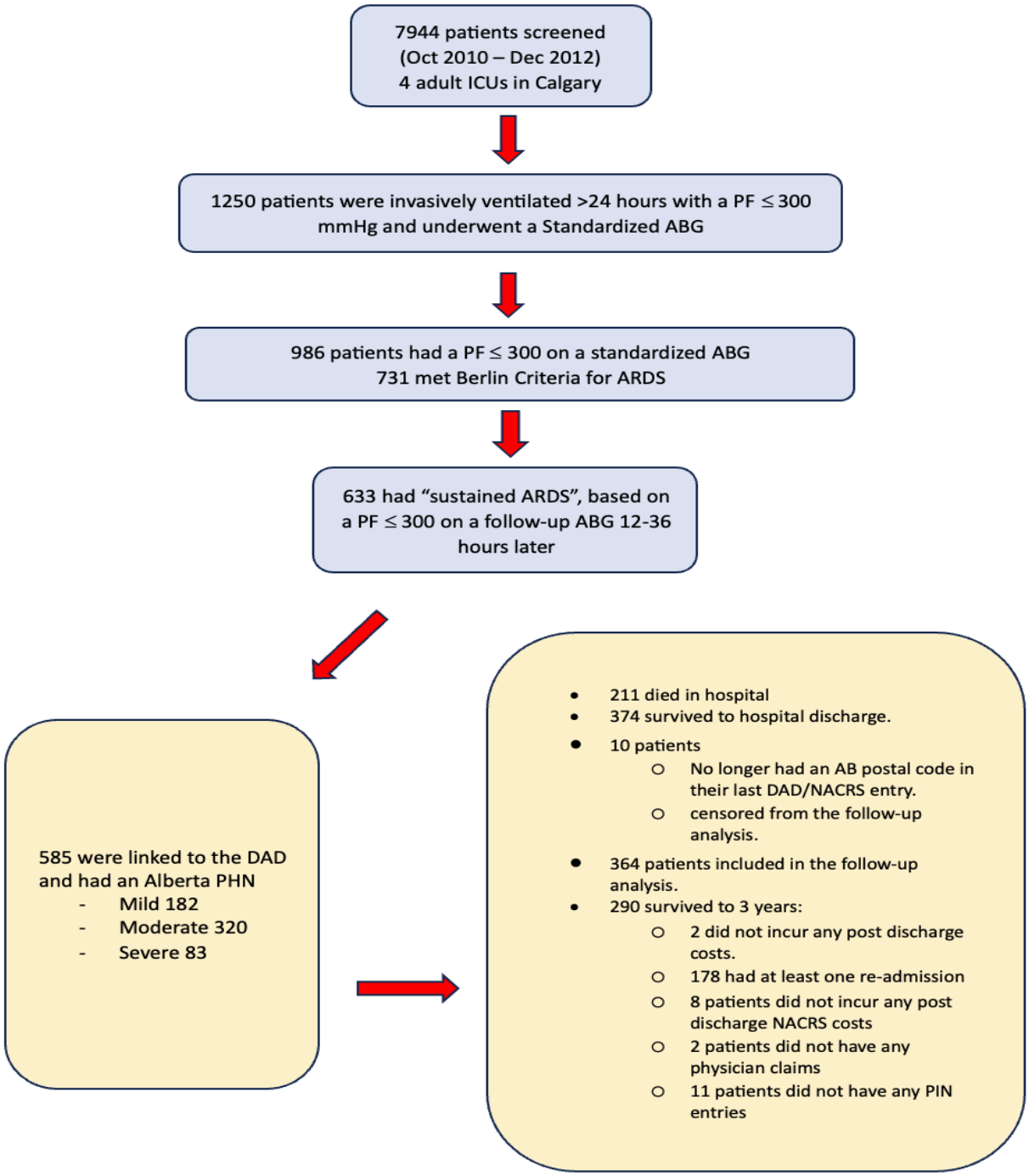

Figure 1: Flowsheet with patient details

AB: Alberta
ABG: Arterial Blood Gas
ARDS : Acute Respiratory Distress Syndrome
DAD: Discharge Abstract Database
ICU: Intensive care unit
NARCS: National Ambulatory Care Reporting System
P/F: $Pa0_2/Fi0_2$ ratio

6.2 Missing Data

There were a total of 40 patients with missing data elements. 11 patients were missing more than one element. The missing data was confined to BMI (31 patients), sex (1 patient), ventilator days (6 patients), admission APACHE II (8 patients), and admission SOFA scores (10 patients). These were considered missing at random and these patients were excluded from any subgroup analyses that included these data points[125]. Their overall costs were included however.

6.3 Index Admission Costs

The demographics and clinical details for the cohort are presented in Table 1. The mean age of the cohort was 58.4 (Standard Deviation [SD] 15.2) and the proportion of females was 0.35. The overall mortality during the index admission was 36%. The proportion of mild, moderate, and severe ARDS was 0.31, 0.55 and 0.14, respectively. The cohort had a significant burden of acute illness with a mean APACHE II score on admission of 21.9 (SD 8.3) and a mean admission SOFA score of 9.4 (SD 3.7). 75% of the patients had a pulmonary risk factor and 57% met criteria for sepsis. 48% of the patients had 2 or more comorbidities. The hospital utilization for the cohort was substantial with a median ICU length of stay of 12 days (Interquartile Range [IQR] 6,18) and a median hospital length of stay of 28 days (IQR 15,53).

	All (585)	Survivors to hospital discharge (374)	Non-survivors to hospital discharge (211)	
Age [mean (SD)]	58.4 (15.2)	56.5(15.4)	61.6(14.3)	P=0.0001*
Sex [female (proportion)]	204 (0.35)	124 (0.33)	80 (0.38)	P=0.229
BMI (Kg/m^2) [mean (SD)]	30 (9.5)	30.9 (10.3)	28.6 (7.7)	P=0.0053*
ARDS severity [n,(proportion)]				
Mild	182 (0.31)	133 (0.73)	49 (0.27)	p<0.0001*
Moderate	320 (0.55)	210 (0.66)	110 (0.34)	
Severe	83 (0.14)	31 (0.37)	52 (0.63)	
SOFA score [mean (SD)][1]	9.4 (3.7)	8.5 (3.1)	10.9 (4.2)	P<0.0001*
Modified SOFA score[2] [mean (SD)][1]	6.4 (3.4)	5.6 (2.8)	7.7 (3.8)	p<0.0001*
APACHE II [mean (SD)][1]	21.9 (8.3)	19.7 (7.3)	25.8 (8.5)	P<0.0001*

ICU LOS (d) [median (IQR)]	12 (6,18)	12 (7,19)	10 (5,18)	p=0.0015*
Ventilator days [median (IQR)]	9 (5,15)	9 (5,15)	9 (5,16)	p=0.5785
Hospital LOS (d) [median (IQR)]	28 (15,53)	34 (20,67)	17 (7,33)	p<0.0001*
Primary pulmonary diagnosis [n,(proportion)]	440 (0.75)	286 (0.76)	154 (0.73)	P=0.349
Sepsis [n,(proportion)]	334 (0.57)	197 (0.53)	137 (0.65)	P=0.004*
Trauma [n,(proportion)]	53 (0.09)	41 (0.11)	12 (0.06)	P=0.033*
Surgery [n,(proportion)]	186 (0.32)	133 (0.36)	53 (0.25)	P=0.009*
≥2 comorbidities [n,(proportion)]	283 (0.48)	168 (0.45)	115 (0.55)	P=0.025*

Table 1: Demographics of the entire cohort. T tests for comparison of means for continuous variables, Wilcoxon rank-sum for medians, and Chi^2 for proportions

* statistically significant

[1] At admission

[2] SOFA without respiratory component

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

The median costs for the index admission, adjusted to 2016 CAD was $105,643 (IQR $58,318, $169,789) 2016 CAD. The breakdown of costs from each costing database is presented in Table 2. The distribution is positively skewed with a mean cost of $146,122 (SD $144,500) 2016 CAD.

	Mean	SD	Median	25th percentile	75th percentile	Obs
Index Admission Total	146,122	144,500	105,643	58,318	169,789	585
Index Admission DAD	126,306	131,580	88,417	48,742	150,297	585
Index Admission NACRS	1,779	1,219	1,506	1,065	2,233	585
Index Admission Claims	18,036	15,860	12,559	8,315	23,037	585

Table 2: Costs for the index admission (Adjusted to 2016 CAD)

DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard deviation

6.3.1 Severity of ARDS

There was an inverse relationship between costs and ARDS severity that was statistically significant. The median total index admission costs for mild ARDS was $113,519 (IQR $63,144, $177,835) 2016 CAD, while for severe ARDS it was $69,037 (IQR $29,037, $155,373) 2016 CAD [p0.0005]. The results by severity are presented in Table 3 and breakdown by costing database is in Tables s1a, s1b and s1c in the supplementary appendix.

Total Index admission costs	Mean	SD	Median	25th percentile	75th percentile	Obs
Mild	161,612	156,732	113,519	63,144	177,835	182
Moderate	143,665	136,656	110,255	61,552	169,819	320
Severe	121,629	143,779	69,131	29,037	155,373	83
p=0.0005						

Table 3: Total index admission costs, by severity (Adjusted to 2016 CAD) with Kruskal-Wallis test of significance

SD: Standard deviation

The demographics by severity are in Table 4. The other indices of illness severity increased with worsening severity of ARDS as did mortality. ICU length of stay also increased with severity but the overall ventilator days did not. There was a shorter hospital length of stay for severe ARDS compared to mild. The patients with severe ARDS were less likely to have surgery as a risk factor.

	Mild (182)	Moderate (320)	Severe (83)	
Age [mean (SD)]	59.1 (15.0)	58.1 (15.3)	57.7 (15.6)	P=0.70
Sex [female (proportion)]	57 (0.31)	109 (0.34)	38 (0.31)	P=0.07
BMI [mean (SD)]	29.9 (8.1)	30.0 (9.6)	30.8 (12.1)	P=0.74
Modified SOFA score[2] [mean (SD)][1]	6.1 (3.0)	6.2 (3.4)	7.6 (3.8)	P=0.0015*
SOFA score [mean (SD)][1]	8.9 (3.3)	9.2 (3.7)	11.1 (4.2)	P<0.00001*
APACHE II [mean (SD)][1]	21.3 (8.1)	21.2 (8.0)	25.7 (9)	P<0.00001*
Hospital mortality [n (proportion)]	49 (0.27)	110 (0.34)	52 (0.63)	P<0.001*
ICU LOS (d) [median (IQR)]	11 (6,16)	12 (7,20)	10 (3,20)	P=0.01*
Ventilator days [median (IQR)]	8 (2,13)	9.0 (6,16)	9 (4,16)	P=0.06
Hospital LOS (d) [median (IQR)]	32 (17,61)	28 (17,51)	15 (7,44)	P=0.0002*

Primary pulmonary diagnosis [n (proportion)]	133 (0.73)	242 (0.76)	65 (0.78)	P=0.64
Sepsis [n (proportion)]	108 (0.59)	175 (0.55)	51 (0.61)	P=0.41
Trauma [n (proportion)]	20 (0.11)	27 (0.08)	6 (0.07)	P=0.52
Surgery [n (proportion)]	77 (0.42)	88 (0.48)	21 (0.25)	P=0.001*
≥2 comorbidities [n (proportion)]	92 (0.51)	154 (0.48)	37 (0.45)	P=0.66

Table 4: Demographics by ARDS severity, entire cohort. ANOVA comparison of means for continuous variables, Kruskal-Wallis for medians, and Chi^2 for proportions.

* statistically significant

[1] At admission

[2] SOFA without respiratory component

ANOVA: Analysis of Variance
APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

6.3.2 Sex

There was no statistically significant difference in costs between males and females. The median costs for females was $98,549 (IQR $55,518, $151,252) 2016 CAD while the costs for males was $109,909 (IQR $59,716, $182,719) 2016 CAD. The results by sex are presented in Table 5 and the breakdown by costing database is in Tables s2a and s2b in the supplementary appendix.

Total Index admission costs	Mean	SD	Median	25th percentile	75th percentile	Obs*
Female	121,474	99,340	98,549	55,518	151,252	204
Male	159,708	162,261	109,909	59,716	182,719	380
p= 0.0614						

Table 5: Cost for index admission by Sex with Wilcoxon Rank Sum test of significance

*one patient with missing sex

SD: Standard deviation

The demographics by sex are in Table 6. While there was no difference in age or mortality, on average, females had a higher BMI. Females also had a higher APACHE II score at admission but

no difference in admission SOFA score or burden of comorbidities. Males were more likely to have had major trauma as a risk factor. There were similar ICU lengths of stay and ventilator days but males had longer hospital lengths of stay.

	Female (204)	Male (380)	
Age [mean (SD)]	59.6 (13.7)	57.8 (15.9)	P=0.16
BMI [mean (SD)]	31.3(10.3)	29.4 (9.1)	P=0.03*
ARDS severity [n, (proportion)]			
Mild	57 (0.28)	125(0.33)	P=0.07
Moderate	109 (0.53)	210 (0.55)	
Severe	38 (0.19)	45 (0.12)	
SOFA score [mean (SD)][1]	9.4 (3.8)	9.4 (3.6)	P=0.97
Modified SOFA score[2] [mean (SD)][1]	6.3 (3.5)	6.4 (3.3)	P=0.66
APACHE II [mean (SD)][1]	22.9 (8.4)	21.3 (8.2)	P=0.03*
Hospital mortality [n (proportion)]	80 (0.39)	130 (0.34)	P=0.23
ICU LOS (d) [median (IQR)]	11 (6,17)	12 (6,20)	P=0.31
Ventilator days [median (IQR)]	9 (5,14)	9 (5,16)	P=0.46
Hospital LOS (d) [median (IQR)]	25 (15,44)	29 (16,64)	P=0.02*
Primary pulmonary diagnosis [n, (proportion)]	153 (0.75)	287 (0.76)	P=0.89
Sepsis [n, (proportion)]	123 (0.6)	211 (0.56)	P=0.27
Trauma [n, (proportion)]	9 (0.04)	44 (0.12)	P=0.04*
Surgery [n, (proportion)]	57 (0.28)	129 (0.34)	P=0.14
≥2 comorbidities [n, (proportion)]	95 (0.47)	188 (0.49)	P=0.50

Table 6: Demographics by Sex, entire cohort. T tests for comparison of means for continuous variables, Wilcoxon rank-sum for medians, and Chi[2] for proportions

[*] statistically significant

[1] At admission

[2] SOFA without respiratory component

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

6.3.3 Hospital survival

There was a significant difference in index admission costs between survivors and non-survivors. The median cost for survivors to hospital discharge was $117,283 (IQR $67,140,

$186,617) 2016 CAD, while for non-survivors to discharge, the median was $78,228 (IQR $39,155, $140,039) 2016 CAD. These results are in Table 7, and the breakdown by costing database is Tables s3a and s3b in the supplementary appendix.

Total Index admission Costs	Mean	SD	Median	25th percentile	75th percentile	Obs
Alive at Hospital Discharge	160,705	147,549	117,283	67,140	186,617	374
Deceased at Hospital Discharge	120,273	135,453	78,228	39,155	140,039	211
p<0.00001						

Table 7: Cost for index admission – By vital status as discharge (Adjusted to 2016 CAD) with Wilcoxon Rank Sum test of significance.

CAD: Canadian Dollars
SD: Standard deviation

The demographics by survival were previously outlined in Table 1. Survivors tended to be younger, have lower indices of illness severity, a higher BMI and a lower burden of comorbidities. They were less likely to have sepsis and surgery as risk factors but more likely to have experienced major trauma. Survivors had longer lengths of stay in both the ICU and the hospital, but similar number of ventilator days.

6.3.4 Multivariate Regression Analysis of Index Costs

A multivariate regression model was constructed using total index admission costs as the dependent variable. The independent variables chosen for the model were described in the methods section. Using untransformed costs as the dependent variable led to a model with residuals that were not normally distributed, both visually (see Figure s1 and s2 in the supplementary appendix) and by the Shapiro-Wilks test for normality ($p<0.0001$). Using costs truncated at the 5th and 95th percentile did not improve the R^2, nor did it improve upon the distribution of the residuals. The proposed substitutions did improve the R^2 values to a degree, but they were all eliminated in the backwards stepwise regression (see supplementary Table s4a).

Log transformation of the total index admission costs led to residuals that were normally distributed, both visually (Figures 2 and 3) and with the Wilks-Shapiro test for normality (p=0.546). Given the better overall fit and normal distribution of the residuals, this is the model that was used.

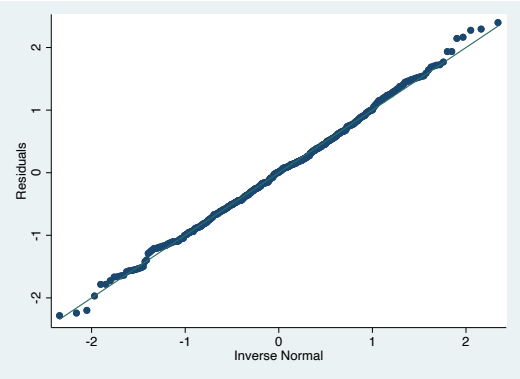

Figure 2: Quantile plot of the residuals vs normal distribution (qnorm) using log transformed total index costs.
Shapiro-Wilks test for normality, p=0.546

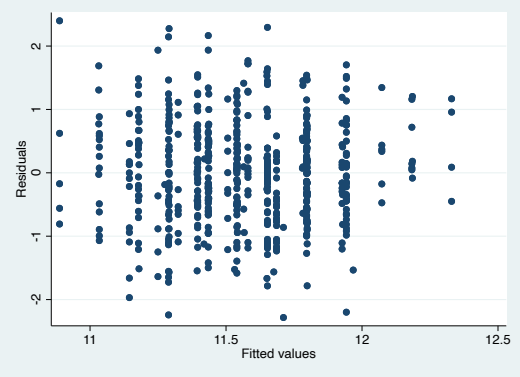

Figure 3: Residuals vs fitted values plot for log transformed total index costs.

Backwards stepwise elimination of candidate independent variables was done until all the remaining variables had p values of <0.05 (See supplementary Table s4b) . The results of the backwards stepwise regression are presented in Table 8. The model reached statistical significance (p<0.00001) with an R^2 value of 0.137, implying that the model explains 13.7% of the variability in costs.

Variable	Coefficient	SE	P value	95% Confidence interval	
BMI≥30	-0.160	0.069	0.021	-0.296	-0.024
ARDS severity	-0.111	0.053	0.038	-0.216	-0.006
Alive at discharge	0.347	0.073	<0.0001	0.204	0.491
Major trauma	0.340	0.120	0.005	0.105	0.576
Surgery	0.339	0.075	<0.0001	0.199	0.486
Sepsis	0.208	0.071	0.004	0.068	0.348
≥2 comorbidities	0.144	0.069	0.038	0.008	0.280
Constant	11.277	0.142	<0.0001	11.000	11.557
R^2 = 0.137 Adjusted R^2=0.126 Sum of squares total 398 Root MSE 0.793 P<0.00001					

Table 8: Regression model for log transformed total index admission costs.

ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
MSE: Mean Squared Error
SE: Standard Error

Variables that are associated with lower index admission costs are worsening ARDS severity and a BMI $\geq$ 30 Kg/m^2. Surviving the index admission, having $\geq$ 2 comorbidities as well as having major trauma, sepsis and surgery are all associated with higher costs.

6.4 Post Discharge Cohort

Of the 374 patients that survived the index admission, 282 patients were alive at 36 months post discharge for a mortality of 22.5% over this period. The median survival time was 15.6 (IQR 6, 28) months. A Kaplan-Meier survival curve for the 36 months is provided in the supplementary appendix (Figure s3). The demographics for the post discharge cohort by survivorship to 3 years, are presented in Table 9. Survivors were younger, more likely to have had surgery as a risk factor for ARDS during the index admission and had fewer comorbidities. They also had a lower APACHE II score during their index admission but their index admission SOFA scores were not different, likely reflecting a difference in the Chronic Health Points portion of the APACHE II score rather than a difference in illness severity. There were no statistically significant differences in the index admission ARDS severity, ventilator days and ICU

and hospital lengths of stay. Having sepsis, trauma, or a primary pulmonary diagnosis as the initial cause of ARDS, did not have any impact on post discharge mortality.

	All Discharged (364)	Survivors to 3 years (282)	Non-survivors to 3 years (82)	
Age [mean (SD)]	56.8 (15.4)	55.6 (15.5)	61.3 (14.2)	P=0.0027*
Sex [female (proportion)]	123 (0.34)	93 (0.33)	30 (0.37)	P=0.543
BMI [mean (SD)]	31.0 (10.4)	31.4 (10.5)	29.8 (10.1)	P=0.2497
ARDS severity [n (proportion)]				
Mild	127 (0.35)	101 (0.80)	26 (0.20)	P=0.586
Moderate	206 (0.57)	159 (0.77)	47 (0.23)	
Severe	31 (0.09)	22 (0.71)	9 (0.29)	
SOFA score [mean (SD)][1]	8.6 (3.1)	8.5 (3.2)	8.9 (2.9)	P=0.2403
APACHE II [mean (SD)][1]	19.7(7.4)	19.2 (7.2)	21.8 (7.8)	P=0.0044*
ICU LOS (d) [median (IQR)]	12 (7,19)	12 (8,19)	10 (6,18)	P=0.06
Ventilator days [median (IQR)]	9 (5,15)	9 (6,15)	7 (5,15)	P=0.09
Hospital LOS (d) [median (IQR)]	34 (20,67)	36 (21,67)	31 (17,53)	P=0.07
Primary pulmonary diagnosis [n (proportion)]	277 (0.76)	210 (0.74)	67 (0.82)	P=0.176
Sepsis [n (proportion)]	191 (0.52)	146 (0.52)	45 (0.55)	P=0.62
Trauma [n (proportion)]	41 (0.11)	35 (0.12)	6 (0.07)	P=0.199
Surgery [n (proportion)]	131 (0.36)	111 (0.39)	20 (0.24)	P=0.013*
≥2 comorbidities [n (proportion)]	163 (0.45)	116 (0.41)	47 (0.57)	P=0.009*

Table 9: Demographics and clinical details for the post discharge cohort. Total cohort and by vital status at 3 years (t test for means, Chi^2 test for proportions, Wilcoxon rank sum for medians).

* statistically significant

[1] At index admission

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

6.5 Post discharge costs

Only 2 patients in the post discharge cohort did not incur any costs. The median costs for all post discharge care across the entire cohort was $38,255 (IQR $14,575, $92,229) 2016 CAD.

These costs were also positively skewed with a mean cost of $77,469 (SD $124,928) 2016 CAD. The total costs and cost per database are presented in Table 10.

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	77,469	124,928	38,255	14,575	92,229	364
DAD	48,865	107,438	13,215	0	56,583	364
NARCS	12,133	21,682	6,937	3,375	13,581	364
Physician Claims	12,123	12,593	8,068	3,953	16,475	364
PIN	4,348	8,298	2,151	589	4,718	364

Table 10: Costs over 36 months post discharge, total and by costing database. Adjusted to 2016 CAD.

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
PIN: Pharmaceutical Information Network
SD: Standard Deviation

Overall, 67% of patients were re-admitted to hospital with median of 2 re-admissions per patient (IQR 1, 4). The median cost per repeat hospitalization was $13,114 (IQR $8,060, $28,804) 2016 CAD. 96% of patients had a visit that was registered in the NARCS database with a median number of visits of 21 (IQR 10, 46). 67% of patients had an emergency room visit with a median of 4 visits in total over the 36 month period (IQR 2, 7). The median cost of an ED visit was $616 (IQR $418, $792) 2016 CAD. The median cost of all other types of NARCS encounters was $207 (IQR $152, $288) 2016 CAD. 99% of patients had at least one physician claim with a similar number of claims for both family physician and specialist claims. For the patients who had a physician claim, the median number of family physician claims was 34 (IQR 17, 67) and 49 (IQR 23, 103) for specialist claims. The median cost for a family physician claim was $59 (IQR $46, $73) 2016 CAD while for a specialist claim it was $104 (IQR $86, $129) 2016 CAD. 95% of the cohort had at least one prescription in the PIN database. Of the patients that filled a prescription, the mean number of prescriptions over the three year period, was 77 (IQR 27, 156). The median cost per prescription, including the dispensing fee was $25 (IQR $18, $41) 2016 CAD. The details related to utilization and costs are in Table 11.

	All (364)	Survivors to 3 years (282)	Non-survivors to 3 years (82)	
Number of patients with re-admission [n(prop)]	245 (0.67)	175 (0.62)	70 (0.85)	p<0.0001*
Number of re-admissions per patient [median (IQR)]	2 (1,4)	2 (1,3)	2 (1,4)	p=0.1186
Cost per hospitalization [median (IQR)]	$13,114 ($8,060,$28,804)	$12,576 ($7,522,$24,932)	$18,205($10,559, $29,334)	p=0.045*
Number of patients with NACRS visits [n(prop)]	351 (0.96)	275 (0.98)	70 (0.85)	p=0.038*
Number of NACRS visits per patient [median (IQR)]	21 (10,46)	24 (11,48)	18 (7,35)	p=0.0368
Number of patients with ED visits [n(prop)]	294 (0.67)	219 (0.78)	75 (0.91)	p=0.005*
Number of ED visits per patient [median (IQR)]	4 (2,7)	4 (2,7)	4 (2,7)	p=0.514
Cost per ED visit [median (IQR)]	$616 ($418,$792)	$545 ($372,$731)	$745 ($579,$892)	p<0.00001*
Cost per NACRS visit excluding ED [median (IQR)]	$207 ($152,$288)	$208 ($158,$285)	$193 ($236,$322)	p=0.4635
Number of patients with physician claims [n(prop)]	362 (0.99)	281 (0.77)	81 (0.99)	p=0.351
Number of patients with GP claims [n(prop)]	357 (0.98)	279 (0.77)	78 (0.95)	p=0.579
Number of GP claims per patient [median (IQR)]	34 (17,67)	33 (27,67)	37 (17,76)	p=0.1009
Number of patients with specialist claims [n(prop)]	355 (0.98)	277 (0.76)	78 (0.95)	p=0.027*
Number of specialist claims per patient [median (IQR)]	49 (23,103)	47 (21,95)	66 (30,125)	p=0.003*
Cost per GP claim [median (IQR)]	$59 ($46,$73)	$56 ($45,$70)	$68 ($30,$125)	p=0.111
Cost per specialist claim [median (IQR)]	$104 ($86,$129)	$103 ($83,$128)	$109 ($95,$135)	p=0.532
Number of patients with PIN entries [n(prop)]	347 (0.95)	272 (0.75)	75 (0.91)	p=0.059
Number of PIN entries per patient [median (IQR)]	77 (27,156)	80 (39,160)	55 (22,134)	p= 0.1915
Cost per PIN entry [median (IQR)]	$25 ($18,$41)	$24 ($18,$38)	$29 ($19,$44)	p=0.1118

Table 11: Utilization and costs per event during the follow-up period for the entire cohort and by survival to 3 years. Adjusted 2016 CAD.

* statistically significant

CAD: Canadian Dollars
DAD: Discharge Abstract Database
ED: Emergency Department
IQR: Interquartile Range
NARCS: National Ambulatory Care Reporting System
PIN: Pharmaceutical Information Network

6.5.1 Post discharge costs and survivorship to 36 months

These was a significant difference in total follow-up costs between survivors and non-survivors to 36 months. The median cost for survivors was $34,419 (IQR $13,255, $76,571) 2016 CAD while the median cost for non-survivors was $56,785 (IQR $25,305, $125,759) 2016 CAD (Table

12). The cost per database by survivorship are in Tables s6a and s6b in the supplementary appendix.

	Mean	SD	Median	25th percentile	75th percentile	Obs
Survivors	73,739	132,837	34,419	13,255	76,571	282
Non-survivors	90,297	92,263	56,785	25,305	125,759	82
Wilcoxon Rank Sum p=0.0038						

Table 12: Total costs over 36 months, by Survivorship to 3 years (Adjusted to 2016 CAD). Wilcoxon rank-sum test of significance.

CAD: Canadian Dollars
SD: Standard Deviation

A higher proportion of non-survivors at 36 months were re-admitted to hospital, 0.85 compared to 0.62 (Table 11). While the median number of hospitalizations amongst those that readmitted were not different between survivors and non-survivors, the median cost per readmission was higher for non-survivors, $18,205 (IQR $10,559, $29,334) compared to $12,576 (IQR $7,522, $24,932) 2016 CAD. A higher proportion of non-survivors had an ED visit (0.91 vs 0.78) with the same number of median visits over the follow-up period (4, IQR 2, 7). The median cost per visit was higher for non-survivors ($745 [IQR $579, $892] vs $545 [IQR $372, $731] 2016 CAD). A higher proportion of non-survivors saw a specialist (0.95 compared to 0.76) and had a higher median number of specialist claims per patient (66 (IQR 30, 125) vs 47 (IQR 21, 95).

6.5.2 Post discharge costs and ARDS severity during the index admission

The total cost over the 36 month follow-up period by ARDS severity during the index admission are presented in Table 13. The difference in post discharge costs by severity were not statistically significant. The median costs for patients with mild ARDS was $40,625 (IQR $15,109, $81,306), moderate $36,680 (IQR $12,969, $93,121), and severe $36,005 (IQR $18,030, $147,205) 2016 CAD. The cost breakdown by database is in Tables s7a, s7b and s7c the supplementary appendix.

	Mean	SD	Median	25th percentile	75th percentile	Obs
Mild	79,875	159,829	40,625	15,109	81,306	127
Moderate	74,852	103,557	36,680	12,969	93,121	206
Severe	85,004	90,245	36,005	18,030	147,205	31
p=0.4315						

Table 13: Total costs over 36 months, by severity with Kruskal-Wallis test of significance. 20016 CAD

CAD: Canadian Dollars
SD: Standard Deviation

The proportion of patients that survived to three years was similar in the three groups (mild 0.8, moderate 0.77, severe 0.71). The demographics and index admission metrics by ARDS severity are in Table 14. There was an increase in ICU length of stay and ventilator days with increasing severity, but the overall median duration of the index admission stay was the same.

	Mild (127)	Moderate (206)	Severe (31)	
Age [mean (SD)]	58.1 (14.5)	56.4 (15.5)	54.8 (18.0)	p=0.4741
Sex (female) [n(prop)]	41 (0.32)	70 (0.34)	12 (0.39)	p=0.792
BMI [mean (SD)]	30.4 (8.6)	31.1 (10.4)	32.5 (15.9)	p=0.5957
Admission SOFA[1] [mean (SD)]	8.4 (3.0)	8.7 (3.2)	8.9 (3.0)	p=0.6307
APACHE II[1] [mean (SD)]	19.8 (7.6)	19.7 (7.4)	20.1 (6.7)	p=0.0537
Alive at 3 years [n(prop)]	101 (0.80)	158 (0.77)	22 (0.71)	P=0.586
ICU Length of stay [median (IQR)]	10 (6,15)	12 (8,20)	20 (11,33)	p=0.0007*
Ventilator Days [median (IQR)]	7 (5,13)	9 (6,16)	14 (8,20)	p=0.0002*
Hospital length of stay [median (IQR)]	35 (21,69)	34 (20,67)	34 (18,79)	p=0.8854
Primary Pulmonary Diagnosis [n(prop)]	92 (0.72)	158 (0.77)	27 (0.87)	p=0.219
Sepsis [n(prop)]	75 (0.59)	102 (0.50)	14 (0.45)	p=0.166
Trauma [n(prop)]	16 (0.13)	23 (0.11)	2 (0.06)	p=0.623
Surgery [n(prop)]	61 (0.48)	61 (0.30)	9 (0.29)	p=0.002
2 or more comorbidities [n(prop)]	58 (0.46)	93 (0.45)	12 (0.390	p=0.773

Table 14: Post discharge demographics by ARDS severity during the index admission.

* statistically significant

[1] At index admission

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

There were no statistically significant differences in readmissions to hospital, ED visits or physician claims across the groups. The post discharge utilization and cost per event are presented in Table 15.

	Mild (127)	Moderate (206)	Severe (31)	
Number of patients with re-admission [n(prop)]	91 (0.72)	131 (0.64)	23 (0.74)	p=0.218
Number of re-admissions per patient [median (IQR)]	2 (1,3)	2 (1,4)	2 (1,4)	p=0.8469
Cost per hospitalization [median (IQR)]	$13,097($7,522,$ 23,420)	$13,518 ($8,060, $30,065)	$11,770($7,887, $26,647)	p=0.4123
Number of patients with NACRS visits [n(prop)]	125 (0.98)	195 (0.95)	31 (1.00)	p=0.106
Number of NACRS visits per patient [median (IQR)]	21 (9,47)	22 (11,46)	20 (9,49)	p=0.9107
Number of patients with ED visits [n(prop)]	106 (0.83)	160 (0.78)	28 (0.90)	p=0.158
Number of ED visits per patient [median (IQR)]	4 (2,6)	4 (2,6)	4 (2,8)	p=0.5018
Cost per ED visit [median (IQR)]	$ 611 ($390, $803)	$610 ($431, $769)	$647 ($513, $869)	p=0.4913
Cost per NACRS visit excluding ED [median (IQR)]	$215 ($164, $318)	$205 ($146, $284)	$198 ($154, $235)	p=0.3714
Number of patients with physician claims [n(prop)]	127 (1.00)	204 (0.99)	31 (1.00)	p=0.426
Number of patients with GP claims [n(prop)]	125 (0.98)	201 (0.98)	31 (1.00)	p=0.617
Number of GP claims per patient [median (IQR)]	35 (16,74)	32 (17,67)	39 (21,66)	p=0.5952
Number of patients with specialist claims [n(prop)]	126 (0.99)	198 (0.96)	31 (1.00)	p=0.137
Number of specialist claims per patient [median (IQR)]	43 (21,94)	52 (25,105)	71 (76)	p=0.2407
Cost per GP claim [median (IQR)]	$59 ($47, $71)	$58 ($46, $73)	$67 ($45, $77)	p=0.6862
Cost per specialist claim [median (IQR)]	$105 ($90, $133)	$104 ($82, $129)	$99 ($87, $125)	p=0.6696
Number of patients with PIN entries [n(prop)]	121 (0.95)	195 (0.95)	31 (1.00)	p=0.422
Number of PIN entries per patient [median (IQR)]	66 (27, 151)	83 (24, 172)	79 (31, 153)	p=0.8942
Cost per PIN entry [median (IQR)]	$25 ($18, $38)	$25 ($18, $41)	$24 ($18, $51)	p=0.8155

Table 15: Utilization and cost per event during the follow-up period for the by ARDS severity during the index admission. Adjusted 2016 CAD.

CAD: Canadian dollars
DAD: Discharge Abstract Database
ED: Emergency Department
IQR: Interquartile Range
NARCS: National Ambulatory Care Reporting System
PIN: Pharmaceutical Information Network

6.5.3 Post discharge costs and Sex

The total costs over the 36 month period by sex are presented in Table 16. The differences in costs between females and males were not statistically significant. The median cost for females was $40,625 (IQR $17,497, $81,306) and for males was $36,771 (IQR $13,255, $95,486) 2016 CAD. The cost breakdown by database is in Tables s8a and s8b in the supplementary appendix.

	Mean	SD	Median	25th percentile	75th percentile	Obs
Female	81,967	110,653	40,625	17,497	81,306	123
Male	75,173	131,780	36,771	13,255	95,486	241
p=0.2799						

Table 16: Total costs over 36 months, by sex (Adjusted to 2016 CAD). Wilcoxon rank-sum test of significance.

CAD: Canadian Dollars
SD: Standard Deviation

The proportion of females and males that survived to 36 months was similar, 0.76 and 0.78 respectively. The demographics and index admission metrics by sex are in Tables 17. There were no statistically significant differences in age, illness severity, burden of comorbidities or ARDS risk factors. While the ICU length of stay and ventilator days were similar by sex, males had a significantly longer overall length of stay in hospital during the index admission (median 29 (IQR 20, 48) days for females, median 37 (IQR 21, 79) days for males).

	Female (123)	Male (241)	
Age [mean (SD)]	56.8 (13.8)	56.90 (16.2)	p=0.9422
BMI [mean (SD)]	32.2 (11.2)	30.40 (10.0)	p=0.1184
ARDS severity [n(prop)]			
Mild	41 (0.33)	86 (0.36)	p=0.792
Moderate	70 (0.57)	136 (0.56)	
Severe	12 (0.10)	19 (0.08)	
Admission SOFA[1] [mean (SD)]	8.3 (2.8)	8.7 (3.3)	p=0.2125
APACHE II[1] [mean (SD)]	20.4 (6.9)	19.4 (7.6)	p=0.2278
Alive at 3 years [n(prop)]	93 (0.76)	189 (0.78)	p=0.543
ICU Length of stay [median (IQR)]	12 (7, 18)	12 (7, 20)	p=0.4272
Ventilator Days [median (IQR)]	8 (6, 14)	9 (5, 15)	p=0.7445
Hospital length of stay [median (IQR)]	29 (20, 48)	37 (21, 79)	p=0.0048*
Primary Pulmonary Diagnosis [n(prop)]	96 (0.78)	181 (0.75)	p=0.533
Sepsis [n(prop)]	72 (0.59)	119 (0.49)	p=0.098
Trauma [n(prop)]	9 (0.07)	32 (0.13)	p=0.089
Surgery [n(prop)]	36 (0.29)	95 (0.39)	p=0.056
2 or more comorbidities [n(prop)]	51 (0.41)	112 (0.46)	p=0.363

Table 17: Post discharge demographics by Sex.

* statistically significant

[1] At index admission

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard deviation
SOFA: Sequential Organ Failure Assessment

There were no statistically significant differences in readmissions to hospital, ED visits or physician claims by sex. The post discharge utilization and cost per event are presented in Table 18.

	Female (123)	Male (241)	
Number of patients with re-admission [n(prop)]	86 (0.70)	159 (0.66)	p=0.448
Number of re-admissions per patient [median (IQR)]	2 (1, 3)	2 (1, 4)	p=0.5226
Cost per hospitalization [median (IQR)]	$12,981 ($7,522, $30,065)	$13,518 ($8,380, $26,400)	p=0.9834
Number of patients with NACRS visits [n(prop)]	121 (0.98)	230 (0.95)	p=0.153
Number of NACRS visits per patient [median (IQR)]	22 (10,46)	21 (10,46)	p=0.7743
Number of patients with ED visits [n(prop)]	101 (0.82)	193 (0.800	p=0.642
Number of ED visits per patient [median (IQR)]	4 (2, 7)	5 (2, 7)	p=0.7804
Cost per ED visit [median (IQR)]	$645 ($474, $823)	$615 ($416, $766)	p=0.2152
Cost per NACRS visit excluding ED [median (IQR)]	$213 ($167, $291)	$200 ($147, $288)	p=0.3857
Number of patients with physician claims [n(prop)]	122 (0.99)	240 (0.99)	p=0.627
Number of patients with GP claims [n(prop)]	121 (0.98)	236 (0.98)	p=0.768
Number of GP claims per patient [median (IQR)]	34 (18,66)	34 (16,69)	p=0.5709
Number of patients with specialist claims [n(prop)]	122 (0.99)	233 (0.97)	p=0.145
Number of specialist claims per patient [median (IQR)]	55 (25, 117)	45 (21, 95)	p=0.0937
Cost per GP claim [median (IQR)]	$61 ($50, $75)	$58 ($46, $73)	p=0.2081
Cost per specialist claim [median (IQR)]	$105 ($80, $130)	$104 ($86, $129)	p=0.8006
Number of patients with PIN entries [n(prop)]	119 (0.97)	228 (0.95)	p=0.36
Number of PIN entries per patient [median (IQR)]	77 (30, 150)	76 (24, 161)	p=0.7514
Cost per PIN entry [median (IQR)]	$27 ($18, $47)	$24 ($18, $38)	p=0.1823

Table 18: Utilization and cost per event during the follow-up period by Sex. Adjusted 2016 CAD.

CAD: Canadian dollars
DAD: Discharge Abstract Database
ED: Emergency Department
IQR: Interquartile Range
NARCS: National Ambulatory Care Reporting System
PIN: Pharmaceutical Information Network

6.5.4 Regression Analysis of Post Discharge Costs

Multiple attempts were made to create a multivariate regression model using total post discharge costs as the dependent variable and the list of independent variables that were described in the methods section. The total outpatient costs were heavily positively skewed with a number of outliers (see Figure 4).

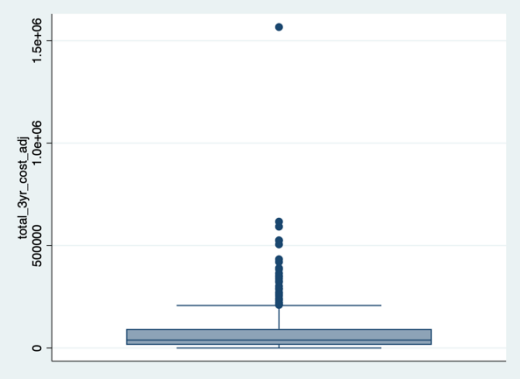

Figure 4: Box plot of total post discharge costs.

Using untransformed costs as the dependent variable led to a model with residuals that were not normally distributed both visually (see Figures s4 and s5 in the supplementary appendix) and using the Shapiro-Wilks test for normality ($p<0.0001$)). Using costs truncated at the 5th and 95th percentile did not improve the R^2, nor did it improve upon the distribution of the residuals. The proposed substitutions did improve the R^2 values to a degree, but they were all eliminated in the backwards stepwise regression (see supplementary Table s9a). Log transformation of the total post discharge cost was undertaken. To facilitate this, one dollar was added to the costs for the two patients that had zero costs. Log transformation led to residuals that were more normally distributed visually (see Figures 5 and 6) but they did not pass the Shapiro-Wilks test for normality ($p <0.0001$).

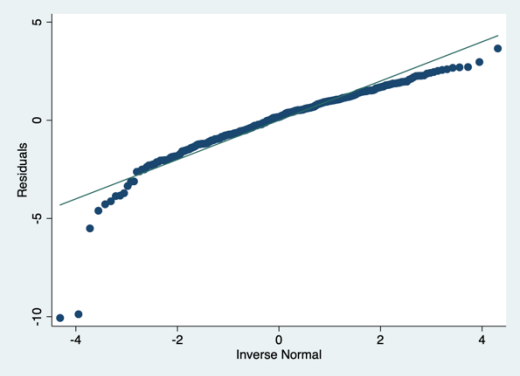

Figure 5: Quantile plot of the residuals vs normal distribution (qnorm) using log transformed total post discharge costs.
Shapiro-Wilks test for normality, p<0.0001

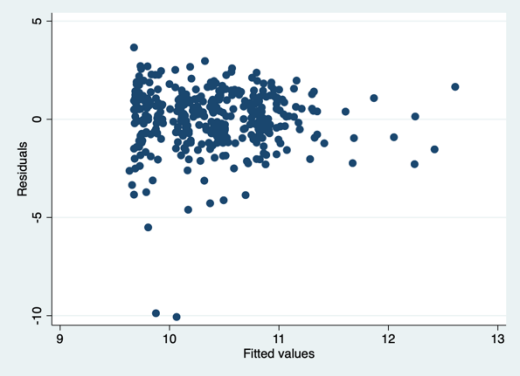

Figure 6: Residuals vs fitted values plot for log transformed total post discharge costs.

Log transformation of the truncated costs (eliminating outliers above the 95th percentile and below the 5th percentile) was also done, but did not normalize the residuals (Shapiro-Wilks p= 0.002, Figures s6 and s7 in supplementary appendix).

Finally, a logistic regression model using a threshold of the 75th percentile for total post discharge costs was created. The goodness of fit was deemed acceptable using the Pearson goodness-of-fit test (Chi^2 = 342.2, p = 0.4230). Backwards stepwise elimination of candidate independent variables was done until all the remaining variables had p values of <0.05 (see supplementary Table s9b). The results of the backwards stepwise regression are presented in Table 19. The final model reached statistical significance (p<0.00001) with an Pseudo R^2 value

of 0.0825, implying that the model only explains 8.25% of the variation in reaching the 75th percentile threshold in costs.

	OR	SE	p	95% confidence intervals	
Greater than 2 comorbidities	1.822	0.471	0.02	1.099	3.023
Died during follow-up	2.258	0.650	0.005	1.285	3.970
Hospital days during the index admission	1.005	0.002	0.017	1.001	1.009
Total Ventilator Days	1.024	0.012	0.039	1.001	1.047
Constant	0.109	0.028	<0.0001	0.066	0.180
p<0.00001 Pseudo R2 0.0825					

Table 19: Results for the logistic regression threshold model (75th percentile).
OR: Odds Ratio
SE: Standard Error

In the final model, the variables that were statistically significant were, having more than 2 comorbidities, dying during the follow-up period, the number of hospital days during the index admission, and the number of ventilator days during the index admission.

Given the potential for collinearity between the number of hospital days and ventilator days, each was removed from the model without a significant change in the odds ratios of the remaining variables. The pseudo R^2 values were lower when they were removed as well. An interaction term between them was added to look for secondary effects. The odds ratio for the interaction term was just below 1 (0.9997), but it was statistically significant (p=0.038).

6.6 Chapter 6: Supplementary Appendix

Mild	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	161,612	156,732	113,519	63,144	177,835	182
Index Admission DAD	140,698	143,517	95,620	52,233	160,411	182
Index Admission NACRS	1,783	1,174	1,592	1,080	2,292	182
Index Admission Claims	19,131	17,138	13,815	8,805	22,284	182

Table s1a: Cost for index admission – Mild ARDS (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation

Moderate	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	143,665	136,656	110,255	61,552	169,819	320
Index Admission DAD	124,159	124,436	90,963	50,159	150508.7	320
Index Admission NACRS	1,795	1,192	1,522	1,071	2,231	320
Index Admission Claims	17,711	14,873	13,038	8,537	23,079	320

Table s1b: Cost for index admission – Moderate ARDS (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation

Severe	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	121,629	143,779	69,131	29,037	155,373	83
Index Admission DAD	103,024	128,749	59,857	17,714	130,079	83
Index Admission NACRS	1,711	1,416	1,408	1,024	1,856	83
Index Admission Claims	16,893	16,679	9,430	6,820	25,222	83

Table s1c: Cost for index admission – Severe ARDS (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation

Female	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	121,474	99,340	98,549	55,518	151,252	204
Index Admission DAD	104,121	90,929	84,103	43,487	132,243	204
Index Admission NACRS	1,689	1,093	1,413	1,024	2,143	204
Index Admission Claims	15,664	11,589	11,727	8,203	19,378	204

Table s2a: Cost for index admission – Female sex (Adjusted to 2016 CAD).

*one patient with missing sex

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation

Male	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	159,708	162,261	109,909	59,716	182,719	380
Index Admission DAD	138,529	147,640	91,944	49,288	158,223	380
Index Admission NACRS	1,828	1,282	1,593	1,071	2,299	380
Index Admission Claims	19,378	17,614	13,498	8,406	24,126	380

Table s2b: Cost for index admission – Male sex (Adjusted to 2016 CAD).

*one patient with missing sex

CAD: Canadian Dollars

DAD: Discharge Abstract Database

NARCS: National Ambulatory Care Reporting System

SD: Standard Deviation

Alive at Discharge	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	160,705	147,549	117,283	67,140	186,617	374
Index Admission DAD	139,771	134,390	98,001	57,148	164,262	374
Index Admission NACRS	1,811	1,216	1,547	1,088	2,356	374
Index Admission Claims	19,123	16,267	13,875	8,814	24,240	374

Table s3a: Cost for index admission – Survivors to discharge (Adjusted to 2016 CAD).

CAD: Canadian Dollars

DAD: Discharge Abstract Database

NARCS: National Ambulatory Care Reporting System

SD: Standard Deviation

Deceased at Discharge	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Index admission costs	120,273	135,453	78,228	39,155	140,039	211
Index Admission DAD	102,439	123,179	65,200	29,253	121,897	211
Index Admission NACRS	1,722	1,224	1,441	1,038	2,102	211
Index Admission Claims	16,112	14,957	11,244	6,993	20,206	211

Table s3b: Cost for index admission – Deceased during index admission (Adjusted to 2016 CAD).

CAD: Canadian Dollars

DAD: Discharge Abstract Database

NARCS: National Ambulatory Care Reporting System

SD: Standard Deviation

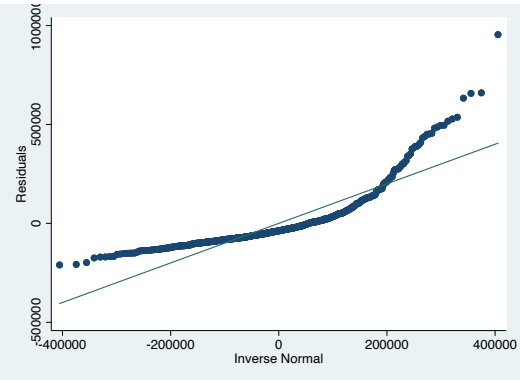

Figure S1: Quantile plot of the residuals vs normal distribution (qnorm) of the residuals using untransformed total index costs.

Shapiro-Wilks test for normality, $p<0.0001$

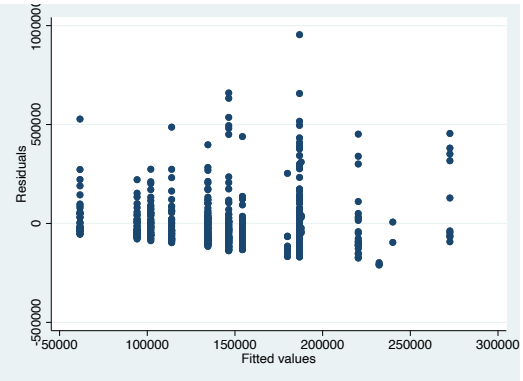

Figure S2: Residuals vs fitted values plot for untransformed total index costs.

					Female			Alive at discharge			Major Trauma			Surgical risk			Sepsis			Constant		
	R2	Adjusted R2	p	AIC	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE
Baseline non transformed model	0.0968	0.089	<0.00001	15486	0.011	-30775.94	12083.56	0.003	36086.73	12097.36	<0.0001	76436.48	20603.85	0.002	39270.85	12612.7	<0.0001	45839.28	11987.31	<0.0001	88331.93	13372.52
Costs truncated below 5th percentile and above 95th	0.089	0.0807	<0.00001	14727	0.01	-32211.64	12529.82	0.024	28679.88	12672.36	<0.0001	80367.58	21259.3	0.008	34692.63	12936.02	<0.0001	47271.28	12473.4	<0.0001	99321.31	14124.88
BMI as a continuous variable	0.1123	0.0875	<0.00001	14719	Eliminated																	
Age as a continous variable	0.1151	0.0904	<0.00001	14717	Eliminated																	
APACHE II for Modified SOFA	0.1102	0.0852	<0.00001	14616	Eliminated																	
Sustained PF (for ARDS severity)	0.1138	0.0891	<0.00001	14718	Eliminated																	
Interaction term Alive at discharge and severity	0.1168	0.0871	<0.00001	14722	Eliminated																	

Table s4a: Regression models for total inpatient costs using truncated costs and substitute candidate independent variables on costs non-transformed regression model.

AIC: Akaike Information Constant
APACHE: Acute Physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
P/F: $Pa0_2/Fi0_2$ Ratio
SE: Standard Error
SOFA: Sequential Organ Failure Assessment

Regression Metrics						Candidate Variables															
R squared	Adj R square	SS Total	Root MSE	p	AIC	age =>65	female sex	BMI (=>30)	Severity	Adj SOFA	Alive at D/C	Pulm risk	Trauma	Pancreatitis	Surgery	Sepsis	>2 comorbid	Cancer	CLD	Alcohol
0.1526	0.1289	398	0.79194	p<0.00001	1330	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
0.1525	0.1305	398	0.79122	p<0.00001	1328	p=0.882	x	x	x	x	x	x	x	x	x	x	x	x	x	x
0.1525	0.1321	398	0.7905	p<0.00001	1326		x	x	x	x	x	x	x	x	x	x	x	x	x	p=0.890
0.1521	0.1333	398	0.78994	p<0.00001	1324		x	x	x	p=0.635	x	x	x	x	x	x	x	x	x	
0.1516	0.1343	398	0.78947	p<0.00001	1322		p=0.545	x	x		x	x	x	x	x	x	x	x	x	
0.1498	0.1341	398	0.78957	p<0.00001	1321			x	x		x	p=0.287	x	x	x	x	x	x	x	
0.146	0.1319	398	0.79061	p<0.00001	1322			x	x		x		x	x	x	x	x	p=0.120		
0.1428	0.1302	398	0.79135	p<0.00001	1322			x	x		x		x	x	x	x	x		p= 0.156	
0.1372	0.1261	398	0.79322	p<0.00001	1323			x	x		x		x	p=0.059	x	x	x			
								p= 0.021	p=0.0038		p=<0.0001		p=0.005		p<0.0001	p= 0.038	p= 0.038			

Table s4b: Results of backward stepwise multivariate regression model for log transformed inpatient costs.

AIC: Akaike Information Constant
BMI: Body Mass Index
CLD: Chronic Liver Disease
D/C: Discharge
MSE: Mean Squared Error
SOFA: Sequential Organ Failure Assessment
SS: Sum of Squares

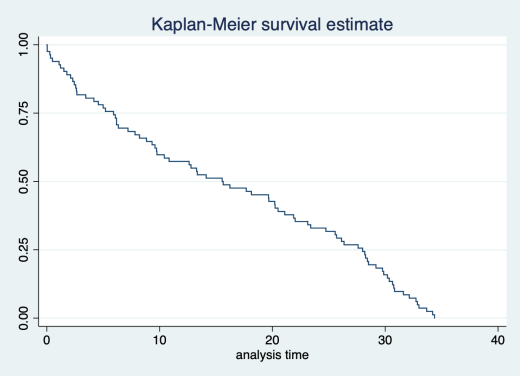

Figure s3: Kaplan-Meier survival curve for the non-survivors in the post discharge cohort.

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	73,739	132,837	34,419	13,255	76,571	282
DAD	45,277	116,122	9,312	0	43,948	282
NARCS	12,209	21,859	7,118	3,634	14,731	282
Physician Claims	11,605	12,526	7,940	3,702	14,779	282
PIN	4,648	9,059	2,219	630	4,799	282

Table s6a: Costs over 36 months – Survivors to 3 years, total and by costing database (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	90,297	92,263	56,785	25,305	125,759	82
DAD	61,207	68,930	38,833	10,728	84,268	82
NARCS	11,871	21,190	6,801	2,416	12,759	82
Physician Claims	13,905	12,738	8,582	4,859	18,747	82
PIN	3,314	4,744	2,004	369	4,506	82

Table s6b: Costs over 36 months – Non-survivors to 3 years, total and by costing database (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

Mild ARDS	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	79,875	159,829	40,625	15,109	81,306	127
DAD	52,122	147,173	14,351	0	57,608	127
NARCS	11,435	12,377	7,524	3,252	14,731	127
Physician Claims	11,978	12,260	8,049	3,896	16,521	127
PIN	4,339	10,296	2,032	532	4,374	127

Table s7a: Costs over 36 months for Mild ARDS, total and by costing database. Adjusted to 2016 CAD.

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	74,852	103,557	36,680	12,969	93,121	206
DAD	45,648	78,710	12,300	0	52,080	206
NARCS	12,730	26,904	6,364	3,475	13,034	206
Physician Claims	12,121	13,082	7,908	3,723	16,078	206
PIN	4,353	7,324	2,029	589	4,905	206

Table s7b: Costs over 36 months for Moderate ARDS, total and by costing database. Adjusted to 2016 CAD.

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	85,004	90,245	36,005	18,030	147,205	31
DAD	56,903	78,616	21,495	0	99,005	31
NARCS	11,024	9,647	8,111	4,193	15,406	31
Physician Claims	12,731	10,854	9,792	4,791	16,078	31
PIN	4,346	4,629	2,930	939	5,329	31

Table s7c: Costs over 36 months for Severe ARDS, total and by costing database. Adjusted to 2016 CAD.

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	81,967	110,653	40,625	17,497	81,306	123
DAD	47,565	78,358	15,906	0	51,458	123
NARCS	14,965	33,351	7,032	3,822	12,935	123
Physician Claims	13,903	13,932	9,335	4,790	17,913	123
PIN	5,534	11,280	2,181	680	5,020	123

Table s8a: Costs over 36 months - Female sex, total and by costing database (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

	Mean	SD	Median	25th percentile	75th percentile	Obs
Total Costs	75,173	131,780	36,771	13,255	95,486	241
DAD	49,529	119,734	12,155	0	63,197	241
NARCS	10,688	11,807	6,847	3,066	14,213	241
Physician Claims	11,215	11,780	7,702	3,142	14,779	241
PIN	3,742	6,195	2,103	496	4,474	241

Table s8b: Costs over 36 months - Male sex, total and by costing database (Adjusted to 2016 CAD).

CAD: Canadian Dollars
DAD: Discharge Abstract Database
NARCS: National Ambulatory Care Reporting System
SD: Standard Deviation
PIN: Pharmaceutical Information Network

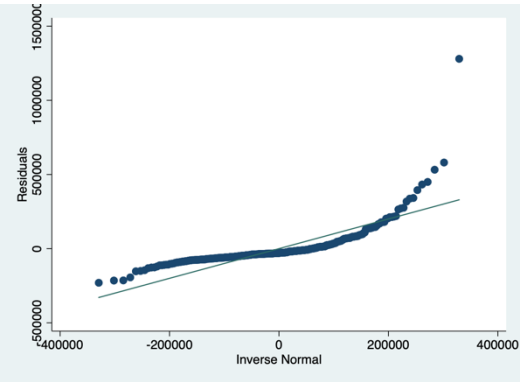

Figure s4: Quantile plot of the residuals vs normal distribution (qnorm) of the residuals using untransformed total post discharge costs.
Shapiro-Wilks test for normality, p<0.0001

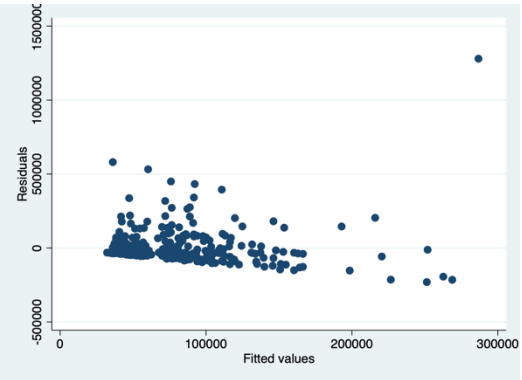

Figure s5: Residuals vs fitted values plot for untransformed total post discharge costs.

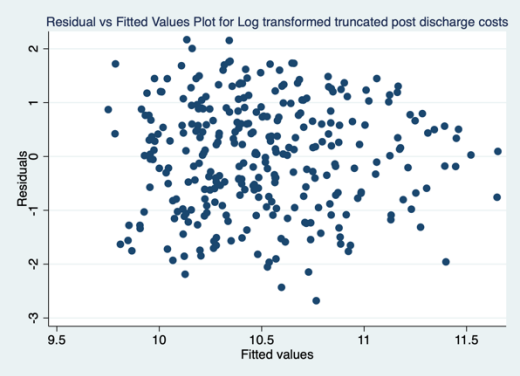

Figure s6: Quantile plot of the residuals vs normal distribution (qnorm) of the residuals using log transformed total post discharge costs, truncated (below 5th and above 95th percentiles). Shapiro-Wilks test for normality, p<0.002

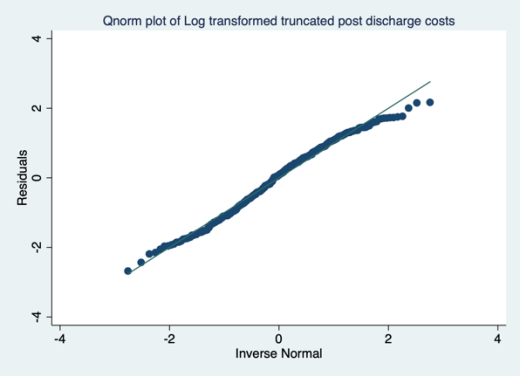

Figure s7: Residuals vs fitted values plot for log transformed total post discharge costs, truncated (below 5th and above 95th percentiles).

					More than 2 Co-morbidities			Hospital days during index			Died at 3 yrs			Total vent days			Sepsis			Constant		
	R2	Adjusted R2	p	AIC	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE
Baseline non transformed model	0.1059	0.1009	<0.00001	9544	36471.2	12544.2	0.004	562.1	98.0	<0.0001										29925.8	9961.8	0.003
Costs truncated below 5th percentile and above 95th	0.0849	0.0763	<0.00001	8023							<0.0001	28822.6	7746.9	<0.0001	1048.6	217.5	0.03	-14072.6	6436.9	48346.8	5728.1	<0.0001
BMI as a continuous variable	0.1467	0.1158	<0.00001	9037	Eliminated																	
Age as a continous variable	0.1418	0.1107	<0.00001	9039	Eliminated																	
Sustained PF (for ARDS severity)	0.1484	0.1176	<0.00001	9037	Eliminated																	

Table s9a: Regression models for total post discharge costs using truncated costs and substitute candidate independent variables on costs non-transformed regression model.

AIC: Akaike Information Constant
ARDS : Acute Respiratory Distress Syndrome
BMI: Body Mass Index
P/F: PaO_2/FiO_2 ratio
SE: Standard Error

Logistic regression for 75th percentile threshold of Total Post Discharge Costs

Regression Metrics			Candidate Variables													
Pseudo R2	p value	AIC	age (=>65)	BMI (=>30)	female sex	Severity	>2 comorbid	Died 3 years	ICU los >10 d	Hosp days	Total vent days	Trauma	Sepsis	Surgery		
0.1049	<0.00001	376	0.753	0.102	0.724	0.337	0.006	0.006	0.415	0.034	0.119	0.378	0.263	0.945		
0.1049	<0.00001	374	0.75	0.102	0.715	0.33	0.006	0.006	0.404	0.034	0.119	0.378	0.253	x		
0.1047	<0.00001	372	x	0.097	0.698	0.326	0.006	0.006	0.395	0.036	0.111	0.348	0.265	x		
0.1043	<0.00001	370	x	0.092	x	0.32	0.006	0.006	0.382	0.039	0.114	0.351	0.275	x		
0.1021	<0.00001	369	x	0.117	x	0.351	0.009	0.006	0.333	0.018	0.113	x	0.197	x		
0.0999	<0.00001	368	x	0.097	x	x	0.011	0.005	0.3	0.024	0.078	x	0.15	x		
0.0971	<0.00001	367	x	0.097	x	x	0.011	0.006	x	0.016	0.019	x	0.152	x		
0.0918	<0.00001	367	x	0.131	x	x	0.011	0.008	x	0.018	0.029	x	x	x		
0.0825	<0.00001	385	x	x	x	x	0.02	0.005	x	0.017	0.039					
Addition of interaction terms															Hospital days*vent days	comorbid>2 *died 3 yr
0.0978	<0.00001	380					0.038	0.004		0.001	0.003				0.038	
0.0846	<0.00001	386					0.014	0.01		0.016	0.035					0.363

Table s9b: Results of backwards stepwise logistic regression model for the 75th percentile threshold for post discharge costs

AIC: Akaike Information Constant
BMI: Body Mass Index
ICU : Intensive Care Unit
LOS: Length of Stay

Chapter 7: Discussion

7.1 Inpatient Costs

This is the first costing study of a cohort of patients with sustained ARDS that were prospectively screened with a standardized protocol. The costs related to inpatient care for this cohort of ARDS patients were significant, and while they are within the range of costs reported in comparable jurisdictions, they are higher than most (see Table 1). There are a number of possible explanations for this difference. It may relate to the Alberta context given the cost of a standard hospital stay provided by CIHI, is higher than the Canadian average[59]. Case mix might also be a contributor given 32% of the patients in this cohort are surgical patients. This risk factor is not frequently reported, and the only one from the comparator groups in Table 1 to do so, had only 13.6% (Marti [2016])[41]. In addition, using sustained ARDS criteria is known to lead to a downward shift in severity, with some patients no longer meeting criteria for ARDS on follow-up ABGs[12, 15]. As such, this cohort may be a more representative cohort of true ARDS without patients that only met criteria transiently.

	Number of patients	Country	Mean	95% Confidence Interval
Boucher (2023)	364	Canada	$146,122	$131,277 - $160,967
Cheung (2006)	109	Canada	$164,361	$142,818 - $192,843
Clermont (2011)	655	US	$98,075	$91,802 - $104,348
Fernando (2021) - control	152	Canada	$58,993	$52,573 - $65,413
Fernando (2021) - lung protective	252	Canada	$48,292	$43,554 - $53,030
Marti (2016)	795	UK	$69,557	$64,492 -$74,658
McAuley (2018)	539	UK	$48,640	$45,493- $51,787
Treggiary (2004)*	151	US	$150,556	$136,024- $165,088

Table 1: Range of mean inpatient costs for the index admission from select[1] studies from the systematic review and from this analysis (converted to 2016 CAD).

[1]All Canadian publications included along with US and European high quality publications (based on modified QHES score)

* median costs and IQR converted to means (SD) by method of Wan

CAD: Canadian Dollars
IQR: Interquartile Range
QHES: Quality of Health Economic Studies
SD: Standard Deviation
US: United States

In this cohort, there was an inverse relationship between severity and costs that was statistically significant. This appears to be, at least in part related increased mortality in the group with severe ARDS that resulted in shorter ICU and hospital lengths of stay. Hospital length of stay is factored into the RIW and a predictor of costs[57]. This finding is in keeping with two other publications, a trauma cohort from the US that used the Berlin criteria[36] and a cohort from the UK[41] that showed a trend towards higher inpatient costs for patients with a P/F < 15 kPa (113 mmHg). Another publication demonstrated the opposite relationship, a separate trauma cohort from the US had increased costs, and longer ICU and hospital LOS for patients with P/F $\leq$ 200 mmHg[88]. Given that trauma patients have a better prognosis overall, that publication may not be representative of a general cohort with ARDS.

Sex was not associated with a statistically significant difference in cost during the index admission. While duration of hospital stay was shorter for females (median 25 [IQR 15, 44] compared to 29 [IQR 16, 64] days), the duration of mechanical ventilation and ICU LOS was the same for males and females. There is a suggestion in the literature that females are less likely to receive low tidal volume ventilation and have worse outcomes compared to males[110], particularly with severe ARDS. There was no mortality difference by sex across the entire cohort in this study.

Costs were also associated with mortality with survivors incurring higher index admission costs compared to non-survivors. This clearly follows lower utilization in terms of shorter ICU and hospital lengths of stay for non-survivors, and is in keeping with findings reported in the higher quality costing studies in the systematic review[28, 41, 86].

The multivariate regression model required log transformation to ensure a normal distribution of the residuals. As such, the relationship between the model and its variables, is to the natural logarithm of total index costs. While the overall model was statistically significant with a p value of <0.0001, the R^2 value explained only 13.7% of the variation in costs, implying that most of

the variation is due to patient factors that were not identified by our candidate variables. A number of variables were statistically significant (p values <0.05) indicating that they are correlated with the log transformed cost. BMI $\geq$ 30 Kg/m^2 and ARDS severity were associated with lower costs. Hospital survival, and having the risk factors of major trauma and surgery, had the strongest associations with increased costs in the model based on the correlation coefficients (0.347, 0.340 and 0.339 respectively). Sepsis and $\geq$2 comorbidities were also associated with higher costs but had lower coefficients.

The association of ARDS severity with lower costs is not surprising given the results of the subgroup analysis. Similarly, survival to hospital discharge had a strong positive correlation to costs when examined independently. Trauma may be understandable given that this risk factor is associated with better outcomes[113]. Major procedures, such as operations are also captured in the DAD, are thus reflected in the RIW[57], and ultimately the cost of the admission. In this cohort, both surgery and trauma as risk factors were associated with lower mortality and longer hospital lengths of stay. Mortality for surgical patients was 28% compared to 40% for those without and median hospital LOS for surgical patients of 33 days (IQR 20, 71) compared to 24 days (IQR 14, 47). Similarly, the mortality for trauma patients was 23% compared to 37% for those without trauma as a risk factor and median hospital length of stay of 47 days (IQR 19, 130) compared to 26 days (IQR 15, 49). Interestingly, the number of ventilator days and ICU LOS were not different for these groups.

The association of increased BMI with lower costs is less well explained by the resource utilization data available. Looking at outcomes and utilization, there were no differences in ICU and hospital LOS or any of the examined risk factors for a BMI cut off of 30 Kg/m^2. (see Table 2). There was also no differences in mortality using this threshold, even though there was a slightly higher BMI overall in survivors (Table 1, results section). The significance of BMI is within the context of the regression model and the other associated variables and the difference in costs must relate to other aspects of intensity reflected in the RIW.

	BMI<30[3] (329)	BMI≥30[3] (225)	P value
Age [mean(SD)]	57.5 (16)	59.7 (13.8)	0.09
Female Sex [n(prop)][1]	103 (0.31)	88 (0.39)	0.06
Mortality [n(prop)]	122 (0.37)	78 (0.35)	0.56
Hospital LOS [median(IQR)] days	29 (16, 59)	28 (16, 47)	0.24
ICU LOS [median (IQR)] days	12 (7, 20)	12 (6, 18)	0.11
Ventilator days [median(IQR)] days[2]	9 (5, 16)	9 (5, 14)	0.16
Trauma [n(prop)]	38 (0.12)	15 (0.07)	0.06
Sepsis [n(prop)]	188 (0.57)	133 (0.59)	0.65
Surgery [n(prop)]	103 (0.31)	73 (0.32)	0.78
Total Index admission Costs			
Mean (SD) 2016 adjusted CAD	$160,023 ($150,909)	$113,959 ($61,807, $190,487)	
Median (IQR) 2016 adjusted CAD	$135,886 ($139,785)	$99,445 ($55,611, $156,093)	0.0341*

Table 2: Demographics and outcomes by BMI < 30 and BMI ≥ 30.

* statistically significant (Wilcoxon Rank Sum)

[1] 1 patient missing sex

[2] 6 patients with missing ventilator days

[3] 31 patients with missing BMI

BMI: Body Mass Index
D: Days
ICU: Intensive care unit
IQR: Interquartile range
LOS: Length of stay
SD: Standard Deviation

There were a number of independent variables that were not associated with costs: modified SOFA score, a primary pulmonary risk factor for ARDS, pancreatitis, malignancy, alcohol abuse and chronic liver disease as specific comorbidities.

Surprisingly, age was also not associated with cost. When the model was changed to include age as a continuous variable or by decile (not shown), the lack of association persisted. Increased age is a predictor for poor outcome in many studies[9, 108, 109] as was the case in this cohort; the mean age in non-survivors to hospital discharge was higher than survivors (61.6 compared to 56.5, see results section, Table 1). On the whole, the age of the cohort was relatively young, possibly representing a degree of selection bias against advanced age when offering ICU admission in the setting of evolving ARDS. It is also possible that elderly patients who were accepted for ICU were more likely to be in prior good health and lacked clinical frailty, further abating any signal related to age. The number of very elderly patient was also

small with only 43 patients (7.4% of the cohort) over 80 years of age. In the context of this economic study, other aspects of patient demographics were more strongly associated with costs.

7.2 Post discharge costs

364 patients were followed for 3 years, making this one of the larger post discharge cohorts in the published literature (See Table 3). Significant health care needs following discharge were seen, with only 2 patients in the entire cohort not incurring any costs. The majority of the costs incurred in this cohort related to re-hospitalization, with 67% of the patients experiencing at least one re-admission. This is in keeping with many of the publications reporting a readmission rates ranging from 24-45%[38, 40, 81] at one year, 39-67%[32, 40, 85] at 2 years and 83%[39] at 5 years.

Compared to other publications, the post discharge costs incurred by this cohort are somewhat higher, but direct comparisons are challenging given the different durations of follow-up and that no other publication followed patients for 3 years (see Table 3).

	Number of patients	Country	Duration of follow-up (yrs)	Mean	95% Confidence Interval
Boucher (2023)	364	Canada	3	$77,469	$63,635-$90,303
Cheung (2006)	109	Canada	2	$36,160	$26,250-$48,915
Clermont (2011)	321	US	1	$38,702	$38,269-$39,135
Herridge (2011)	83	Canada	1	$25,033 (no SD provided)	
Herridge (2011)	63-69	Canada	5	$11,092-$6,246 (mean cost per year (years 2-5)	
Marti (2016)	388	UK	1	$7,274	$5,393-$9,156
Ruhl (2017)	764	US	1	$46,491	$40,932- $52,050
Ruhl (2017)*	138	US	2	$40,698	$33,377-$48,020
Ruhl (2015)*	123	US	5	$93,298	$71,585-$115,011

Table 3: Comparison[1] of post discharge costs, all costs converted to 2016 CAD for comparison.

[1]All studies in the systematic review that reported on post discharge costs are included.

* median costs and IQR converted to means (SD) by method of Wan

CAD: Canadian Dollars
IQR: Interquartile Range
SD: Standard Deviation
US: United States

Even with the challenges in direct comparisons, there were some studies, including the other two Canadian studies that showed significantly lower costs compared to ours[32, 41, 43, 44]. This was related in part to lower rates of re-admissions over the follow-up period compared to our and other cohorts. It is noteworthy that patients in these studies were followed prospectively, both in person and by telephone, requiring direct consent. In addition, utilization was established, in large part, through interviews or questionnaires. This may have led to a biased sample and underreporting of health service utilization.

Mortality in the 36 months after the index admission was associated with increased costs over the follow-up period with a higher proportion of those that died requiring re-hospitalization and with a higher cost per admission. Similarly, there was an increased proportion with ED visits and a higher cost per encounter for non-survivors.

Severity did not appear to be associated with increased costs during the follow-up period, but the number of patients with severe ARDS was small compared to the overall cohort (36 out of 364). Sex was also not associated with increased cost in the post discharge period.

Despite several attempts to manipulate the 3 year post discharge costs, a linear regression model that had normally distributed residuals was not achieved. In the end, a logistic regression model using a 75th percentile threshold was used[106]. While this produced a model with a better overall fit, it resulted in a loss of information in that the model only informed on costs above the 75th percentile. The model was overall statistically significant but the Pseudo R^2 was quite low (0.0825), meaning that this model explains only a small portion of variation in costs, and that most of the variation in costs is due to patient factors that were not identified through the candidate variables.

Dying within the follow-up period had the highest odds ratio for reaching the 75th percentile threshold (OR 2.3), followed by $\geq$ 2 comorbidities (OR 1.8). Dying in the post discharge period had a strong association with overall costs in the subgroup analysis when examined

independently. Most of the publications that looked at post discharge costs, did so on survivors only and the distinction between post discharge costs by survivorship has not previously been reported in this population . The relationship between higher costs and increased comorbidities is consistent with other publications in ARDS patients[44, 85].

Total hospital days and total ventilator days were also associated with an increase in odds of reaching the 75th percentile threshold (OR 1.005 and 1.024 respectively). While these odd ratios are small, they represent an incremental change per day and could potentially be important for long stays in hospital and prolonged time on the ventilator. While these variables did not appear to be colinear, there was a weak, but statistically significant interaction effect between them (OR 0.9997, p = 0.038). This implies that as these values increase, they have a tempering effect on each other. This association has not been previously reported in the ARDS costing literature. Longer duration of ventilation is associated with 1 and 5-year mortality in ARDS patients[122] and duration of hospitalization in ARDS has been associated with re-admission[120] and 1 year mortality[22].

There were a number of independent variables not associated with reaching the 75th percentile of post discharge costs: ARDS severity during the index admission, sex, and the ARDS risk factors of trauma, surgery and sepsis.

ICU LOS $\geq$ 10 days was not associated with increased costs either, indicating that the other markers of ventilator and hospital days were more significant. In ARDS patients, ICU LOS has been associated with increased risk of readmission and post discharge costs[40, 85]. In these publications, duration of mechanical ventilation and hospital stay were not included in their regression analyses. Overall duration of hospital stay was included in a publication looking at 5 year costs and did not find it to be a significant variable[39]. It is possible that there is a diminishing importance of these two variables as they relate to cost and utilization over time and that the association become less important beyond three years.

As with inpatient costs, age did not have a statistically significant correlation with increased cost in the post discharge period. Non-survivors during the three year period were older with a mean age of 61.3 (SD 14.2) years, compared to 56.8 (SD 15.4) years in survivors. Despite mortality having a strong association with costs, age was not an independent risk factor. This is consistent with the other publications that have reported on post discharge costs in ARDS survivors[39, 40, 44, 85]. This lack of association is likely multifactorial. Overall, the mean age in this cohort is relatively low and any signal related to age may be missed due to a smaller population. This is also a biased cohort given that they have survived a critical illness, and are not representative of the general population. In survivors of ARDS, there are factors other than age that are more strongly associated with increased post discharge costs.

7.3 Strengths

One of the strengths of this study is that it is a sizeable cohort of ARDS patients and the only costing study in patients with sustained ARDS who were identified prospectively using a standardized screening protocol. Costs during the index admission were also complete and it is a representative population, with resource use and mortality in keeping with many publications. As such, the costs identified here should give a reasonable estimate of costs in the Canadian, and in particular, the Alberta context.

It is also one of the larger outpatient cohorts and had a longer follow-up than what has been reported in much of the published literature. In addition, the entire cohort was used rather than a select group that agreed to detailed follow-up. This is arguably a more representative cohort and free from selection bias that might be present in a cohort that agrees to be followed. These biases might include missing patients from rural areas, those with lower socioeconomic status, those with language barriers, and possibly other underprivileged groups from a health equity standpoint. While the group was not followed prospectively, it is likely that all health services covered by the Province were captured. Only patients with Alberta Health care and valid postal codes were kept in the group. Costs were reported on all patients, not just those who survived.

7.4 Limitations

While the inpatient cohort was identified prospectively and in a standardized fashion, there were 48 patients from the original cohort of 633 patients with sustained ARDS that did not have a linkage to the DAD or a valid Alberta PHN. They were excluded from the economic analysis as costs could not be obtained. The reasons for the lack of linkage is not clear and whether the exclusion of these patients introduced a bias into the cohort is unknown.

CMG+ case mix costing was used to calculate costs. Micro-costing is considered to be the gold standard in costing methodologies. For cardiovascular diagnoses in Alberta, CMG+ costing has been shown to provide estimates that are closer to micro-costing compared to DRG methodology, but it does still underestimate costs[65]. Whether this finding is applicable to ARDS patients is not known. Our review of the costing literature in ARDS did not find any head to head comparisons of methodology in this population and the context and heterogeneity of the studies in this review were too diverse to undertake a meta-analysis of costs and methodologies to better examine any potential bias. While case mix methodologies may be more representative of typical cases, there are a number of outlier patients with significant costs, and there is a risk that these are underestimated. More advanced therapies for ARDS may not be well captured by case mix methodology (prolonged use of inhaled pulmonary vasodilators, neuromuscular blockers, and advanced therapies such as extracorporeal membrane oxygenation [ECMO]). While the methodology used may have underestimated costs for inpatient care in this cohort, they are nonetheless substantial and on par, if not higher than other publications.

The outpatient cohort was not followed prospectively and resource use and costs rely on administrative data. While all activity covered under the provincial health care system should be captured, any public health care received outside of the Province or though other funding mechanisms would be not have been captured (Workman's Compensation Board claims,

Federal claims through Justice, or any out of Province utilization). We also did not capture costs related to rehabilitation facilities and long term care following discharge, had we done so, the post discharge costs would have no doubt been higher.

In this analysis, the economic perspective of the public payer was chosen such that all costs borne by the patient and society at large were not accounted. Accordingly, the costs reported are then an underestimate of the true cost of ARDS[126]. Costs related to informal caregivers[28] and lost wages[83, 84] along with any other costs incurred by the patient and third party insurers, also account for an important financial burden that was not captured in this analysis.

The decision to remove the 10 patients who did not have a valid postal code at the end of the follow-up period has the potential to bias the results. Out of the 10 patients, only one did not incur any costs and 2 died during the follow-up period. The median number of months that these patients contributed costs over the 36 month period, was 30 (IQR 16,35). However, a sensitivity analysis that included them did not change the overall mean cost significantly and the median cost remained the same (Table 4).

	Mean	SD	Median	25th percentile	75th percentile	Obs
Censored cohort	$78,364	$125,416	$38,515	$15,044	$92,938	364
Full cohort	$77,793	$124,197	$38,515	$14,734	$92,314	374

Table 4: Sensitivity analysis comparing total 3 yr. post discharge costs with the full and censored cohort. 2016 CAD.

CAD: Canadian Dollars
SD: Standard Deviation

The regression models for both inpatient and post discharge costs required transformation and manipulation to achieve a workable model. Log transformation makes the coefficients of the inpatient costs challenging to interpret and the threshold model used for post discharge cost only informs the threshold. A larger sample size may have helped avoid these issues.

7.5 Applicability

This work contributes to the current body of literature by providing a comprehensive cost analysis of prospectively identified, sustained ARDS patients in the Canadian and Albertan context. It also has a comprehensive analysis of post discharge costs over a 3-year period, notwithstanding some of the limitations discussed. Given that focusing on sustained ARDS ensures a cohort of patients with true ARDS, the costs identified for this cohort may be more representative of actual costs than previous publications, particularly in the Canadian context. The post discharge costs should also be representative of the true costs over this time period given that all survivors were followed and all of their publicly funded health care utilization should have been captured. This costing information will be important to economic modeling analyses looking at cost effectiveness of new therapies or large quality improvement projects seeking to improve the care provided to these patients. One such project is currently underway in the Province. "Venting Wisely" is a provincial quality improvement project aimed at improving the provision of evidence-based ventilator management for patients with ARDS.[127] Understanding the cost effectiveness of this and other treatment modalities will be of value to decision makers as they make policy decisions in the setting of limited resources.

The costs and utilization for this population are substantial and this leads to the question of how to reduce them. In terms of inpatient costs, the variables from the multivariate analysis are, for the most part, not modifiable. Surgery and trauma were associated with increased costs and appeared to be partially based on bed utilization; hospital lengths of stay were statistically longer for both of these groups. Interestingly, the duration of ICU LOS and ventilator days were not. Based on this data, programs aimed at reducing costs might best target the post ICU care of surgical and trauma patients who had ARDS. Efforts to rehabilitate these patients more intensely during and after their ICU admission may reduce their overall hospital length of stay and costs. Most of the evidenced-based therapies that have been shown to improve outcome in ARDS have focused on adherence to safe ventilation practices and care bundles in the ICU[24].

The cost impact of these have not been evaluated. The only publication that reported on costs related to low tidal volume ventilation compared to higher tidal volume ventilation specifically, did report better outcomes, shorter duration of mechanical ventilation, shorter lengths of stay, and lower costs in the low tidal volume group[43]. This was an observational study of patients in the emergency department and thus limited in its generalizability and in making conclusions related to causality.

Post discharge costs are similarly associated with risk factors that are not modifiable: burden of comorbidities and hospital length of stay during the index admission. Programs that support ARDS survivors with these factors after discharge may prevent re-admissions and costs. Post discharge follow-up studies are lacking that look at longer term outcomes and costs for patients who have received evidence based ARDS care compared to those that did not.

7.5.1 ARDS as a syndrome

ARDS is a syndrome that results from a complication of another diagnosis. When using case mix (CMG+) methods, the whole hospital encounter is costed and the contribution of ARDS to overall cost, cannot be specifically elucidated. In some cases, such as those associated with surgery and trauma, it is not clear if costs are being driven by the presence of ARDS or by other aspects of service intensity and cost per service. Surgical procedures are captured in the CMG+ methodology certainly contribute to this group being associated with higher expenditures. With the limitations of the study design, we were not able to evaluate the attributable cost of ARDS. Study designs that propensity match patients would be better suited to determine the attributable costs related to ARDS in a given population.

7.5.2 The applicability to Covid-19

ARDS due to infection with Covid 19, is a relatively new spectrum of this syndrome. While it is inviting to suggest that costing analyses apply to this entity as well, there is little data published

on the cost of Covid-19 related ARDS. The systematic review was completed prior to the pandemic but a subsequent search of the literature found only two publications that reported on costs related to Covid ICU admissions. Both are large database studies and as they do not specifically report on patients with ARDS, would not have met inclusion criteria for the systematic review. One is a study of patients admitted to ICU in San Paolo, Brazil between March and June of 2020, and found a mean cost per admission of $20,003 USD (2020)[128]. It is not clear, but unlikely that all these patients met criteria for ARDS. The other is from the US and used the Premier Healthcare Database (PHD), a database that includes approximately 20% of all hospital admissions in the US. They identified 173,942 Covid-related hospital admission between April 1 to 31 October 2020 of which 16.9% were admitted to the ICU and received mechanical ventilation. The hospital costs for patients that were admitted to ICU and received mechanical ventilation were a mean $78,425 (SD $81,621) USD (2020) and a median cost of $54,402 (IQR $66, 797) USD (2020). As with the previous study, the prevalence of ARDS in this population is not reported[129]. Despite the limitations of both of these studies, when put into context of the systematic review, the costs reported are comparable to those previously reported in both the US and Brazil.

There may be value in evaluating the costs related to Covid-19 ARDS specifically given the burden that it has put on health systems globally. There is some evidence to support that length of stay and mortality are comparable to non-Covid-19 ARDS[49, 50] but other aspects of utilization may be different, such as the need for transfusion and dialysis[50]. Certainly, the majority of patient with Covid-19 ARDS, will likely have this as a main diagnosis, in contrast to surgical or trauma patients who are more likely to develop ARDS as a complication of their initial diagnosis[50]. However, the landscape and spectrum of severity have changed over time with vaccination and viral mutations that have both resulted in a reduced risk of severe disease[130, 131]. Clinical and economic studies during early waves of the pandemic may not be reflective of the endemic state and subsequent waves.

Post discharge costs for patients with ARDS from Covid-19 may also not be applicable to this cohort. Post Covid syndrome has been well described[132, 133] and is associated with increased health care utilization following the hospital admission[134]. Post ICU syndrome has been identified in patients suffering from critical illness[135] and whether this entity is different for survivors of patients with ARDS and those with Covid-19 in particular is not known.

7.6 Conclusion

The health utilization and costs incurred in the provision of care for patients with ARDS is substantial. This burden is present both during the index hospital admission and beyond. The results of this costing analysis are marginally higher than others in the reported literature. This may reflect differences related to the screening process and definition of sustained ARDS, or may be a reflection of the costs of care in the Province of Alberta.

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