DEFINING PEDIATRIC CHRONIC CRITICAL ILLNESS

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements of the Degree of Master of Science

MASTER OF SCIENCE (2021)

Health Research Methodology

McMaster University

Hamilton, Ontario, Canada

TITLE: Defining Pediatric Chronic Critical Illness

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NUMBER OF PAGES: ix, 56

ABSTRACT

Introduction: Improvements in the delivery of intensive care have led to a growing number of children with chronic medical conditions at significant risk of recurrent and prolonged critical illness. These patients are increasingly described as having pediatric chronic critical illness (CCI). To date, pediatric CCI is without an accepted consensus case definition.

Objective: To evaluate how pediatric CCI has been defined in the current literature, including the concept of prolonged PICU admission, and describe the methodologies used to develop any existing definitions. Secondary aims included describing patient characteristics and outcomes evaluated in included studies.

Methods: We searched four electronic databases for studies evaluating children identified with "CCI." We also searched for studies describing prolonged PICU admission, as this concept is related to pediatric CCI. We developed a hybrid crowdsourcing and machine-learning (ML) methodology to complete citation screening. Screening and data abstraction were performed by two reviewers, independently and in duplicate. We completed data abstraction including details of population definitions, demographic and clinical characteristics of children with CCI, and outcomes evaluated.

Results: Twenty-eight reviewers from 11 countries performed citation screening, with a mean sensitivity of 92%. Of 24,729 unique citations assessed for eligibility, 453 full-texts were reviewed and 67 studies were included. Of these, 12 studies (18%) defined CCI, most commonly by a prolonged PICU length of stay (LOS), either in isolation or in addition related to medical complexity patient characteristics and/or readmissions rate. The concept of prolonged PICU admission was defined in an additional 55 (82%) studies by a median of 14 days (range, 1 day-6 weeks).

Conclusion: To our knowledge, this scoping review provides the most comprehensive epidemiologic evidence addressing pediatric CCI. Our results suggest a uniform consensus definition is needed in order to advance this emerging and important area of pediatric critical care research.

297/300 words

ACKNOWLEDGEMENTS

I am extremely grateful for the unwavering support and commitment of my supervisor, Karen Choong, which predates this thesis by more than 10 years. Like a Jedi Master, she is patient, wise, and above all, prioritizes the success of her padawans. Without "KC," I would not have realized most (if not all) of the success I have experienced in my academic career to date. I aspire to be even half the clinician-investigator she is.

To my thesis committee, Bram, Dayre, and Joyce, thank you for your advice, your time, and your commitment to my graduate school training and this important work. Despite challenges, including the COVID-19 pandemic, you never wavered in your commitment. You have helped me blaze a forward (but never straight) path as a clinician-investigator.

I must also thank the other members of the Pediatric CCI Scoping Review Team. Katie O'Hearn, Sanket Patel, and Ravi Rachamalla, thank you for guiding the design and execution of a hybrid crowdsourcing and machine-learning review. Neethi Pinto and Rachel Couban, thank you for your content and methods expertise that allowed us to conduct a rigorous scoping review. And of course, many thanks to the international #PedsICU community for welcoming and supporting this important project.

Finally, I am most thankful for the love and support of my partner, Katarina, who has lived this experience has much as I have and maybe more. You have never doubted my ability to achieve in my scholarly and career pursuits, even when I have. I could not ask for a better partner in life.

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LIST OF ABBREVIATIONS

BOW, Bag of Words

CCI, chronic critical illness

CICU, cardiac intensive care unit

ICU, intensive care unit

LOS, length of stay

ML, machine-learning

NICU, neonatal intensive care unit

PICU, pediatric intensive care unit

PRISMA, Preferred Reporting Items for Systematic Previews and Meta-Analyses

TF-IDF, Term Frequency-Inverse Document Frequency

DECLARATION OF ACADEMIC ACHIEVEMENT

I, David Zorko, declare this thesis to be my own work. My supervisor (Dr. Karen Choong) and the members of my supervisory committee (Drs. Bram Rochwerg, Dayre McNally, and Joyce Obeid) have provided guidance and support at all stages of this thesis. I completed all of the research work.

CHAPTER I: INTRODUCTION

1.1. Background

Due to improvements in the delivery of intensive care over the past two decades, the survival of even the most critically ill children has increased and overall mortality in the pediatric intensive care unit (PICU) has decreased to 2-4%[1,2]. An unintended consequence of this success has been a shift in the population of patients admitted to the PICU, with an increasing number of children with chronic complex medical conditions and significant long-term morbidities following critical illness. Children with chronic complex medical conditions now account for more than 50% of children admitted to the PICU[1,3-5]. In contrast to the decreasing mortality amongst all-comers in the PICU over the past two decades, mortality for children with chronic and complex medical conditions has remained relatively unchanged[6] and has even increased in those who have prolonged PICU admissions[7,8]. Furthermore, these patients' risk of mortality persists well beyond their PICU stay[9,10], with the highest risk patients being those with chronic complex conditions and repeated PICU admissions[11].

This population shift in the PICU has been further elucidated by a growing body of research evaluating morbidity-based outcomes in critical care survivors. Traditionally, mortality has been the quality indicator for critical care, and as a result, residual morbidities and long-term functional impairments in PICU survivors were unrecognized. However, we have increasingly realized that the morbidities encountered by child survivors of critical illness translate to important long-term healthcare needs outside of the PICU, with up to an estimated 82% of survivors having new functional disabilities, 16% having new medical devices/technologies, and 28% having new homecare equipment[9,10,12]. As a result, the demand and complexity of pediatric

critical care is evolving—yesterday's PICU survivor is progressively becoming tomorrow's PICU patient.

1.2. Chronic critical illness in children

There is growing recognition that a subset of pediatric critical illness survivors experience persistent multi-organ system dysfunction and functional morbidities following critical illness that subsequently render them with either a prolonged need for critical care support as inpatients, or dependence on medical technology in order to be cared for as outpatients[13 14]. These children are increasingly referred to as having chronic critical illness (CCI)[15 16]. Despite being a uniquely high-risk population in the PICU, research on pediatric CCI remains limited and this patient population has been under-studied, in large part due to the lack of an accepted consensus case definition.

Developing a consensus definition for pediatric CCI is necessary as this is an emerging area of high research importance in pediatric critical care[15 17]. The prevalence of children with CCI appears to be increasing[1 8 16], and they are the subpopulation of critically ill children with the highest risk of readmission and highest PICU and long-term mortality[7 8]. These children also experience persistent long-term morbidities that require significant use of PICU resources, as evidenced by their use of organ support technologies, and prolonged and/or recurrent PICU admissions[7 8 16 18]. Current PICU systems are not well adapted to the longitudinal and comprehensive care needs of children with CCI, which may further prolong their hospital stay[19-21]. They are also identified as having the highest risk of prolonged residual morbidity after critical illness[22], placing significant strain on both the healthcare system and caregivers of children with CCI. Healthcare provider and family burnout may result from the chronic, intense,

and complex care needs of children with CCI, as well as an overall uncertainty regarding the outcomes of these children[23]. These convergent and complex issues related to pediatric CCI has numerous potential implications for research of high-impact to patients, families, healthcare providers, and society.

To date, references to pediatric CCI have identified this subgroup of patients by a prolonged length of stay (LOS) in PICU (i.e., "long-stay patients") that ranges from days to months[4 6-8 15 16 24]. Others have suggested that a definition of pediatric CCI should expand beyond PICU LOS, and incorporate concepts of a frail health state and ongoing need for critical care as evidence by frequent PICU readmissions and medical complexity and morbidity status[15]. The variability in description of the pediatric CCI population makes it unclear if the current working definitions are referring to the same patient demographic or indeed adequately captures the concept of persistent or prolonged critical illness.

In order to position the field of pediatric CCI research to systematically evaluate this important patient population, a consistent approach is needed with respect to the population that is being described and studied. A consensus case definition is much needed and an essential pre-requisite to evaluating the epidemiology and the outcomes of these children (i.e., their long-term outcomes and quality of life), family-important outcomes, and the impact of this patient population on PICU and overall healthcare. Only then is it possible to determine modifiable risk factors for poor patient outcomes, and develop and evaluate interventions to improve the care and survivorship for this important PICU patient population.

1.3. Scoping review method for emerging fields

A scoping review is a useful evidence synthesis methodology for examining emerging areas of research, as its major objective is to broadly synthesize a body of literature in a given field. Scoping reviews can be used to map the types of evidence in a given field, identify and describe key characteristics related to a concept, and identify knowledge gaps for further study[25]. Consequently, scoping reviews are well-suited and often performed to clarify definitions on a research topic and/or identify key constructs to inform the development of a consensus definition for a topic[25 26]. The first scoping review methodology was proposed by Arksey and O'Malley in 2005[27] and numerous others have subsequently elaborated upon the rigorous conduct and reporting of scoping reviews[26 28-30].

A key first step to developing a consensus case definition for pediatric CCI, is a systematic synthesis of the current literature to identify any existing definitions, and in their absence, key terms and constructs to inform the development of a working definition. To date, such a review of the literature on children with CCI has not been performed, and the body of work describing pediatric CCI is expected to be heterogenous and complex. Therefore, a scoping review is the most appropriate evidence synthesis design for our study objectives.

1.4. Pediatric chronic critical illness scoping review objectives

The primary aim of this scoping review is to evaluate how pediatric CCI is defined in the current literature. This scoping review will also evaluate how the concept of prolonged PICU admission is defined in the current literature, as this has been identified as an important qualifier for pediatric CCI.

Secondary aims of this scoping review are to describe the methodologies used to develop and/or validate any existing definitions of pediatric CCI. We will also seek to describe the prevalence of CCI in the PICU based on existing definitions, and describe key demographic and clinical characteristics of the patient populations studied. Finally, we will describe the nature of the reported outcomes in children with CCI.

CHAPTER II: SCOPING REVIEW METHODS

2.1. Protocol

This original scoping review followed standard methodology first proposed by Arksey and O'Malley[27], and elaborated upon by others[28 29]. The protocol was designed a priori and was reported in accordance with the Preferred Reporting Items for Systematic Previews and Meta-Analyses (PRISMA) extension for Scoping Reviews (**Appendix A**)[30]. We uploaded the protocol as a pre-print to Open Science Framework (OSF) on 1 February 2021[31], which is also currently under review for print publication. We planned to document protocol amendments in OSF with date, description, and rationale. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

2.2. Eligibility criteria

2.2.1. Types of participants/population

We included studies that evaluated critically ill children (i.e., <18 years old) admitted to any PICU, explicitly identified with "chronic critical illness." We also included studies that evaluated prolonged, protracted, chronic or long-stay PICU admission, as this concept has been identified as an important qualifier for pediatric CCI. We excluded records if they: i) evaluated adult or neonatal ICU populations only, or included children among these populations but do not report separate data for children; ii) evaluated pediatric patients in intermediate care, step-down, high-dependency or chronic ventilator/respiratory units, or; iii) did not include or reference a definition of pediatric CCI or prolonged PICU admission, as applicable to the study (e.g., as a case definition in a prevalence study).

2.2.2. Types of interventions, comparators and outcomes

We did not apply any restrictions with regard to interventions, comparators or outcomes.

2.2.3. Types of publications

We included observational and experimental studies, qualitative studies, and protocols that provided a working definition of pediatric CCI or prolonged PICU admission. We excluded literature reviews, unpublished literature, editorials, commentaries and opinion pieces, conference proceedings, abstracts, and books. Given the emerging nature and recent recognition of CCI in children, we excluded records published prior to 1990. We excluded studies that were not published in English or French.

2.3. Information sources and search strategy

We developed a preliminary search strategy in two electronic databases (Medline and CINAHL) and piloted this in consultation with a health research librarian (RC). We developed the final search strategy in Medline, had it peer-reviewed by two additional health research librarians not involved in the study, and then translated it into the other databases, as appropriate (**Table 1**). We searched the following electronic databases from their dates of inception to March 3, 2021: Ovid Medline, Embase, CINAHL, and Web of Science. We reviewed the reference lists of all included studies to identify any studies that may have evaded the final database search.

Table 1. Search strategy (Medline)

Database
OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy
1. intensive care units/ and (child* or pediatric or paediatric).mp. 2. Intensive Care Units, Pediatric/ 3. PICU.mp. 4. ((p?ediatric* or child or children*) adj3 (acute* or critical* or intens*)).mp. 5. or/1-4 6. exp Critical Care/ 7. Critical Illness/ 8. (critical* or intens*).mp. 9. or/6-8 10. exp Chronic Disease/ 11. "Length of Stay"/ 12. ((long or duration or length) adj3 (stay or hospitali*)).mp. 13. or/10-12 14. 5 and 9 and 13 15. ((chronic* or persist* or long term or longterm or long-stay or prolong* or protract* or extend* or extensive or lengthy or difficult*) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. 16. 5 and 15 17. 14 or 16 18. ((p?ediatric* or child or children*) adj5 (chronic* or persist* or long term or longterm or prolong* or protract* or extend* or extensive or lengthy or difficult* or ((long or duration) adj3 stay)) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. 19. 17 or 18

2.4. Study selection

2.4.1. Search strategy and study selection criteria piloting

The team used an iterative approach to evaluate and refine the preliminary search strategy and study selection criteria. Using the results of the preliminary search strategy, four members of the core study team independently reviewed an initial set of 100 randomly selected citations using the initial study selection criteria. Each record was reviewed in triplicate. We screened the 100 citations in two steps (title and abstract, then full text), discussed discrepancies, and refined the eligibility criteria. The lead investigator (DZ) reviewed the reference lists of studies meeting all inclusion criteria, identified any relevant studies, and together with the health sciences librarian refined the search strategy if these relevant studies were missed by the database search. Following this initial round, we reevaluated the revised study selection criteria using a second set of 100 random citations assessed independently and in triplicate. The conflict rate was 45.5% (5/11 full texts) and 7.7% (1/13 full texts) at full text assessment during the two iterative piloting rounds, respectively. Following these two iterative piloting rounds, the team established consensus on study selection criteria. A total of eight eligible studies were identified during piloting.

2.4.2. Crowdsourcing

Given the large number of citations identified in the final search strategy, we employed a hybrid approach consisting of crowdsourcing and a machine-learning (ML) algorithm to expedite citation screening. Crowdsourcing methodology for systematic reviews has been previously validated[32 33] and employed in a variety of health research reviews in order to accelerate citation screening and provide more timely research output, while still allowing for rigorous review

conduct[34-36]. We recruited a curated crowd of 32 reviewers with content and/or methodological expertise from social media (using the hashtags #PedsICU, #PICSp, and #CCI), email, and a dedicated study crowdsourcing event webpage[37]. We also recruited reviewers through presentations of the project at the Canadian Critical Care Trials Group (February 1, 2021) and Pediatric Acute Lung Injury and Sepsis Investigators group (March 8-9, 2021). Authorship incentives were offered to crowd reviewers who achieved specific screening milestones (i.e., group authorship if ≥500 abstracts and ≥50 full texts screened, named authorship if ≥1000 abstracts, ≥100 full texts screened and participated in data abstraction).

Prior to formal screening, prospective reviewers were provided with a copy of the protocol and study selection criteria. Prospective reviewers first performed screening on a test set designed using the piloted study selection criteria[38]. The test set contained 100 citations from the piloting phase with 10 eligible (true positive) citations. Reviewers needed to achieve a sensitivity ≥80% on the test set to be given access to the full set of study records. Reviewers who did not achieve ≥80% sensitivity were provided with additional training prior to being given access to the full set of study records.

We used a dedicated channel on Slack (Slack Technologies, San Francisco, CA), a cloud-based team communication platform, to streamline study progress updates and reviewer communication[39 40]. The various software platforms and applications used in the conduct of this scoping review are summarized in **Appendix B.**

2.4.3. Machine-learning algorithm

ML algorithms are increasingly used to assist in citation screening for systematic reviews, particularly in large reviews[41-44]. We developed an ML algorithm to semi-automate

citation screening for this scoping review at the title and abstract stage only, consistent with previously described approaches (**Figure 1**)[44]. The independent and duplicate screening of at least 4000 citations through to full text by crowd members constituted the "training set" that was used to evaluate five ML algorithms (Bag of Words [BOW], Term Frequency-Inverse Document Frequency [TF-IDF], Word to Vector, Document to Vector, Fast Text). These algorithms rank each citation by relevance based on the text captured in the study selection criteria and project goal, with the highest-ranking citations being retained based upon a threshold set by the investigator (e.g., a threshold of 70% would retain the highest ranking 30% of citations).

We selected the two highest performing algorithms from the training set and evaluated their sensitivity and specificity, at a variety of thresholds, when used alone and when combined with a single human reviewer to screen citations. We also separately evaluated the performance of the two highest performing ML algorithms for citations without an abstract (i.e., title only) to determine whether a unique threshold would be required. For both ML algorithms, we determined the threshold at which sensitivity exceeded 95% when used in combination with a single human reviewer. This approach was consistent with the individual sensitivity of "expert" reviewers, as described in previous studies[33 36 45 46].

Once developed, we evaluated the performance of the two candidate ML algorithms on an additional "validation set" constituting at least 2000 citations screened independently in duplicate by crowd members. We a priori determined that we would proceed with duplicate independent human assessment of citations above the selected threshold score, and machine plus one independent human assessment for citations below the threshold score. We also planned to apply an additional lower threshold score if the sensitivity data for the candidate ML algorithms

consistently exceeded our sensitivity goal (i.e., 95%). This lower threshold served to exclude the most to exclude the most irrelevant citations through assessment by the ML algorithm alone.

2.4.4. Integration of hybrid crowdsourcing and machine-learning algorithm citation screening

The integration of crowdsourcing and ML-algorithm methods into citation screening in this scoping review is outlined in **Figure 1**. We downloaded records from the electronic search into Endnote for duplicate removal and exported the citation list for screening to insightScope (www.insightscope.ca)[47], a platform for executing large reviews through crowdsourcing. We uploaded citation abstracts and full text articles with inclusion and exclusion criteria to insightScope. Screening was performed in two steps (title and abstract, then full text) against inclusion criteria by two independent reviewers. We recorded reasons for exclusion for citations excluded at full text screening. All screening conflicts (either between two humans or machine and one human) were resolved by third party adjudication by the core study team, as required.

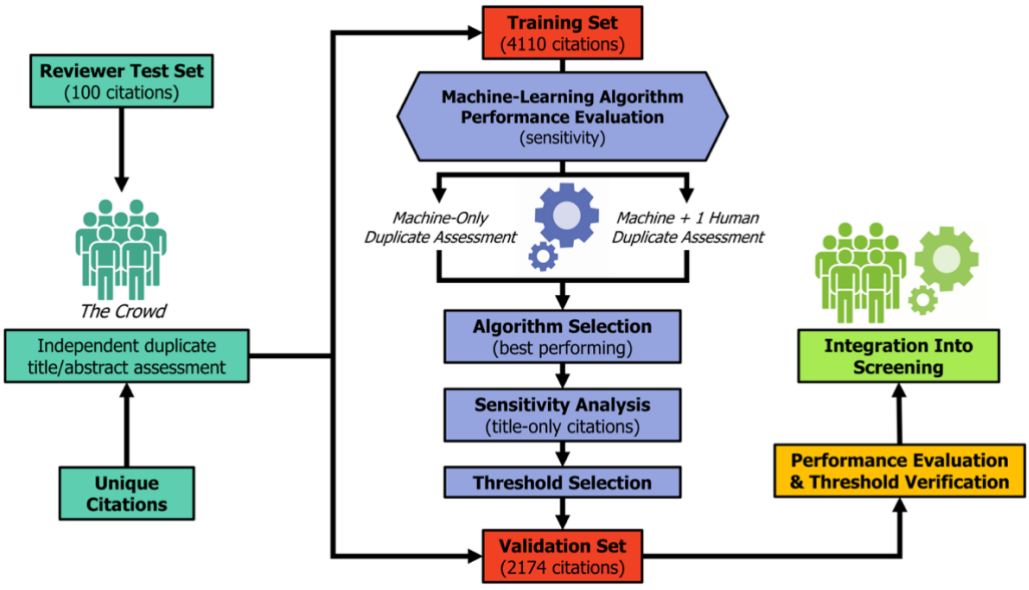


Figure 1. Integration of crowdsourcing and machine-learning in the scoping review

2.5. Data abstraction and data charting

We performed data abstraction using piloted electronic data abstraction forms created in insightScope. The data abstraction forms were created by one investigator (DZ) and piloted by five members of the core investigative team against a total of eight eligible studies. We describe data items in **Table 2**. Prior to formal data abstraction, we provided all data abstractors with training which included a data abstraction manual and training video. Data was abstracted by two independent reviewers from the crowd, independently and in duplicate. We abstracted data from the full text publication and any related publications, referenced published protocols, or supplementary materials. Where necessary, one reviewer abstracted graphical data using SourceForge Plot Digitizer (http://plotdigitizer.sourceforge.net) which was checked by the second reviewer for accuracy. The study lead (DZ) resolved conflicts in data abstraction, as required. In the event of missing or unclear data related to our outcomes of interest, we planned to make a maximum of three attempts to contact study authors for clarification.

2.6. Results synthesis

We reported data related to study characteristics descriptively using counts with percentages or measures of central tendency and variance (e.g., means/medians with standard deviations/interquartile range), as appropriate. Data related to study population definitions, and the methodologies used to derive them, were summarized narratively in tables. We grouped included studies into one of the two definition domains based on their explicitly identified study population of interest (i.e., CCI or prolonged PICU admission) and summarized data for each, separately. Statistical analyses were performed with IBM SPSS Statistics, Version 26 (IBM, Armonk, NY). In keeping with the descriptive objectives of this scoping review, we did not plan

quantitative analyses, risk of bias assessment for included studies, or certainty of evidence assessment[25 29].

In future analyses, we will summarize patient characteristics and outcomes evaluated in included studies. Data regarding patient characteristics will be reported descriptively and summarized qualitatively, as appropriate. We plan to categorize patient- and family-based outcomes evaluated in included studies as per the domains of the PICU Core Outcome Set[48] (overall health, cognitive function, physical function, emotional function), as applicable, to help formulate a priority agenda for future research.

Table 2. Data items

Characteristic	Data Items
Study Characteristics	• Author name and contact information • Title • Country of origin • Journal and year of publication • Study design • Clinical setting/type of PICU (e.g., medical-surgical, cardiac only, neuro-PICU, etc.) • Total patients included • Study period (dates)
Study Population Definition	• Definition of pediatric CCI (e.g., as defined by study or referenced from another publication) • Definition of prolonged PICU/long-stay admission (e.g., duration, as defined by study or referenced from another publication) • If and how the definition was developed and/or validated by the primary study • Prevalence of study participants with CCI or prolonged PICU admission, as applicable to the study
Study Population Demographics and Characteristics	• Age, sex • Reason for PICU admission • Source of PICU admission (e.g., emergency department, NICU, floor/step-down unit, etc.) • Functional status characteristics (using validated tools, as categorized by the article) • Severity of illness characteristics (using validated tools, as categorized by the article) • Comorbidity/medical complexity status, including if and how patient medical complexity/comorbidity was described in the study • Prevalence and types of organ support technologies in study participants (e.g., mechanical ventilation, feeding support, circulatory support [vasoactive drugs, ECMO, ventricular assist device], extrarenal filtration) • Types of study participants (e.g., children with CCI/prolonged PICU admission, families/siblings, healthcare providers)
Outcomes Evaluated	• Stated primary outcome, including how it was measured and result • Patient-specific outcomes, including mortality (PICU, hospital, overall), discharge disposition (e.g., high-dependency unit, ward, rehabilitation facility, home), health-related quality of life • Family outcomes (any, as categorized by the article) • Healthcare provider outcomes (any, as categorized by the article) • Healthcare system outcomes, including LOS (PICU, hospital), PICU bed-day use/consumption, PICU re-admission rate/occurrence, PICU cost analyses

Legend: CCI, chronic critical illness; ECMO, extracorporeal membrane oxygenation; LOS, length of stay; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit

2.7. Funding

This scoping review did not receive any specific funding. David Zorko was supported by a Canadian Institutes of Health Research (CIHR) Canada Graduate Scholarship – Master's Award (award number n/a). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the protocol.

2.8. Acknowledgements

The authors would like to express their appreciation to Christine Neilson, MLIS (University of Manitoba) and Dr. Margaret Sampson, MLIS (Children's Hospital of Eastern Ontario) for providing peer-review of our Medline search strategy. The authors also express their gratitude to Sanket Patel (Team Lead, insightScope) and Ravichandra Rachamalla (Machine-Learning Development, insightScope) for their work related to developing, validating, and integrating the machine-learning algorithms in this review.

CHAPTER III: SCOPING REVIEW PRELIMINARY RESULTS

3.1. Crowdsourcing recruitment and reviewer characteristics

A total of 32 crowdsourced reviewers completed the test set of 100 citations, achieving a mean (SD) sensitivity of 91.6% (0.09). Two reviewers with exactly 70% sensitivity on the test set were provided additional training on the study protocol and study selection criteria prior to citation screening. Of these, 28 reviewers, with a test set sensitivity of 92.1% (0.09), participated in citation screening. The number of citations screened by reviewers was 996 (549) and 28 (31) at title/abstract and full-text stages, respectively. Reviewers originated from Canada (n=9), United States (n=7), Saudi Arabia (n=2), Singapore (n=2), United Kingdom (n=2), Brazil (n=1), Colombia (n=1), Ireland (n=1), Italy (n=1), South Africa (n=1), and Spain (n=1).

The majority of crowd reviewers were staff physicians (n=15, 53.6%), of which 13 were based in the PICU. All crowd reviewers had at least some previous research experience, 11 (39.3%) had graduate-level training, and 20 (71.4%) had prior systematic or scoping review experience. Five reviewers (17.8%) had no previous clinical or research experience in the PICU. Most crowd reviewers learned about this scoping review through Twitter (n=15, 47.6%), word of mouth (n=7, 33.3%), or participation in PICU trials networks/communities (n=5, 53.6%). The top reported reasons for participating in this scoping review were interest in the research topic (n=17, 60.7%), collaboration with our specific research team (n=13, 46.4%), and potential for future collaborations (n=13, 46.4%).

3.2. Machine-learning algorithm development and validation

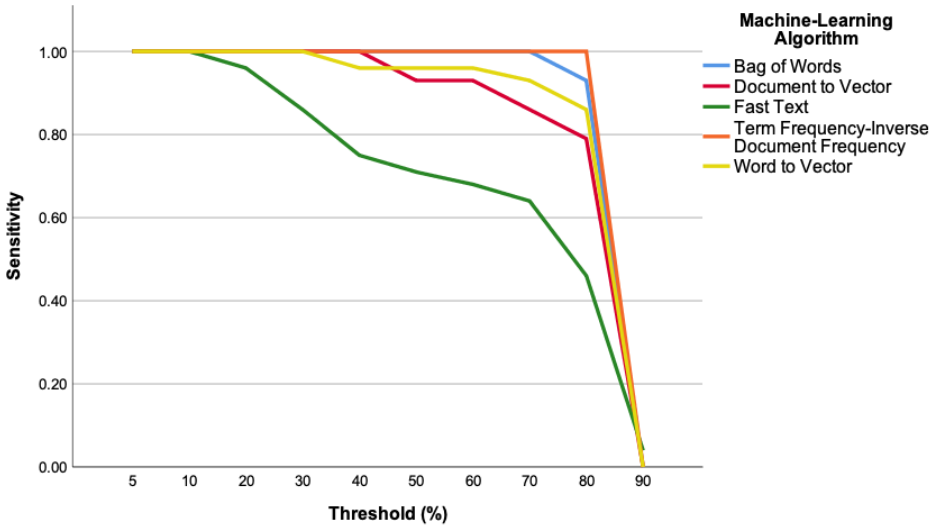
As a prerequisite to incorporating an ML algorithm into citation screening, we determined the optimal algorithm and sensitivity threshold to operationalize. The sensitivities of

the five evaluated ML algorithms when used alone or in combination with a single human reviewer to assess citations from the training set are presented in **Figure 2A** and **2B**, respectively. The 4110-citation training set included 28 citations meeting inclusion criteria following assessment by two reviewers after full-text review (i.e., true positives). The two highest-performing ML algorithms were BOW and TF-IDF, demonstrating 93% and 100% sensitivity at a threshold of 80% when citation assessments were performed by the ML algorithm alone. Sensitives for both these ML algorithms were 100% at a threshold of 80% when citations assessments were performed by ML algorithm in combination with a single human reviewer.

Additional sensitivity analyses were performed using the BOW and TF-IDF algorithms using a separate threshold for citations without an abstract (i.e., title only) in order to evaluate if these citations perform differently. For this analysis, the threshold for citations with an abstract was fixed at 70% and the threshold for citations without an abstract was varied between 30%, 50%, and 70%. The BOW and TF-IDF algorithms demonstrated sensitivities of 100% at all dual threshold combinations (i.e., 70/30, 70/50, and 70/70), both when citations were assessed by the ML algorithm alone or in combination with a single human reviewer.

We subsequently evaluated the BOW and TF-IDF ML algorithms on a validation set of 2174 additional citations. Again, these citations were screened independently and in duplicate by the crowd reviewers. The validation set included 9 unique citations meeting inclusion criteria. Based on the sensitivity results from the training set, we chose to apply the following conservative thresholds to evaluate performance on the validation set: 70% for citations with an abstract, and 50% for citations with title only. Both the BOW and TF-IDF algorithms demonstrated a sensitivity of 92% when citations were assessed by the ML algorithm alone, and a sensitivity of 100% when used in combination with a single human reviewer.

A.



B.

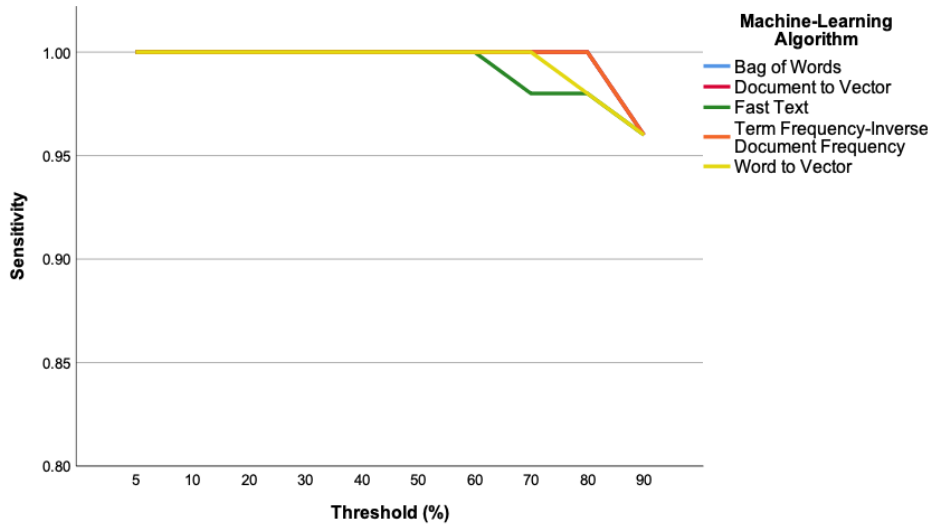


Figure 2. Machine-learning algorithm training set performance
A. Sensitivities of five machine-learning algorithms by threshold (machine-only citation assessment). Legend: Bag of Words and Term Frequency-Inverse Document Frequency demonstrate the highest sensitivities up to a threshold of 80%.
B. Sensitivities of five machine-learning algorithms by threshold (machine plus one human reviewer citation assessment). Legend: Doc2Vec line overlaps with TFIDF. Bag of Words line overlaps with TFIDF, demonstrating a sensitivity of 100% at a threshold of 80%.

In addition to sensitivity, we also evaluated ML algorithm specificity. Both TF-IDF and BOW algorithms demonstrated a similar specificity at the 70% threshold (i.e., 0.68), but the TF-

IDF algorithm retained 3 less false positive citations. Given this marginally better performance, the final ML algorithm selected was TF-IDF. Considering that ML algorithms are relatively novel in the conduct of large scoping reviews, we adopted a conservative approach to integrating the algorithm into citation screening for the remaining 18,325 citations. For citations with an abstract, the following three thresholds were selected:

i. citations with a score ≥70% threshold were assessed by duplicate independent human assessment;
ii. citations with a score between 30% to 70% threshold were assessed by machine plus one independent human assessment, and;
iii. citations with a score ≤30% threshold were assessed by machine-only assessment.

For citations without an abstract (i.e., title only), we similarly adopted a conservative approach by selecting a 50% threshold and no option for machine-only citation assessment. Therefore, citations with a score ≥50% threshold were assessed by duplicate independent human assessment, and citations with a score <50% threshold were assessed by machine plus one independent human assessment.

3.3. Study identification

Of 40,698 records identified through the initial database search (**Appendix C**), 24,728 unique citations were reviewed for eligibility. Citation assessments were performed by two independent human reviewers for 12,116 (49.0%) citations, machine and one human reviewer for 7,854 citations (31.8%), and ML algorithm alone for 4,758 (19.2%) citations. We assessed 449 full-texts, from which 63 studies were eligible and included in the results synthesis[6-8 16 18-20 22-24]

[49-101]. The duration of the review, from citation screening start (March 5, 2021) to completion of data abstraction (April 16, 2021), was 42 days.

Four additional studies[102-105] were identified from reference lists of the initial 63 included studies that met inclusion criteria, totalling 67 eligible studies included in the results synthesis: two citations were excluded by duplicate human assessment at the title/abstract stage, one citation was excluded following third reviewer arbitration at the title/abstract stage, and one citation was missed by the search strategy. The cumulative flow diagram of study selection is illustrated in **Figure 3**. The three citations excluded by human assessments made no reference to prolonged PICU admission in the title or abstract; however, upon review of their full text, these studies conducted some analyses on prolonged stay PICU patients and PICU LOS threshold to define prolonged PICU admission.

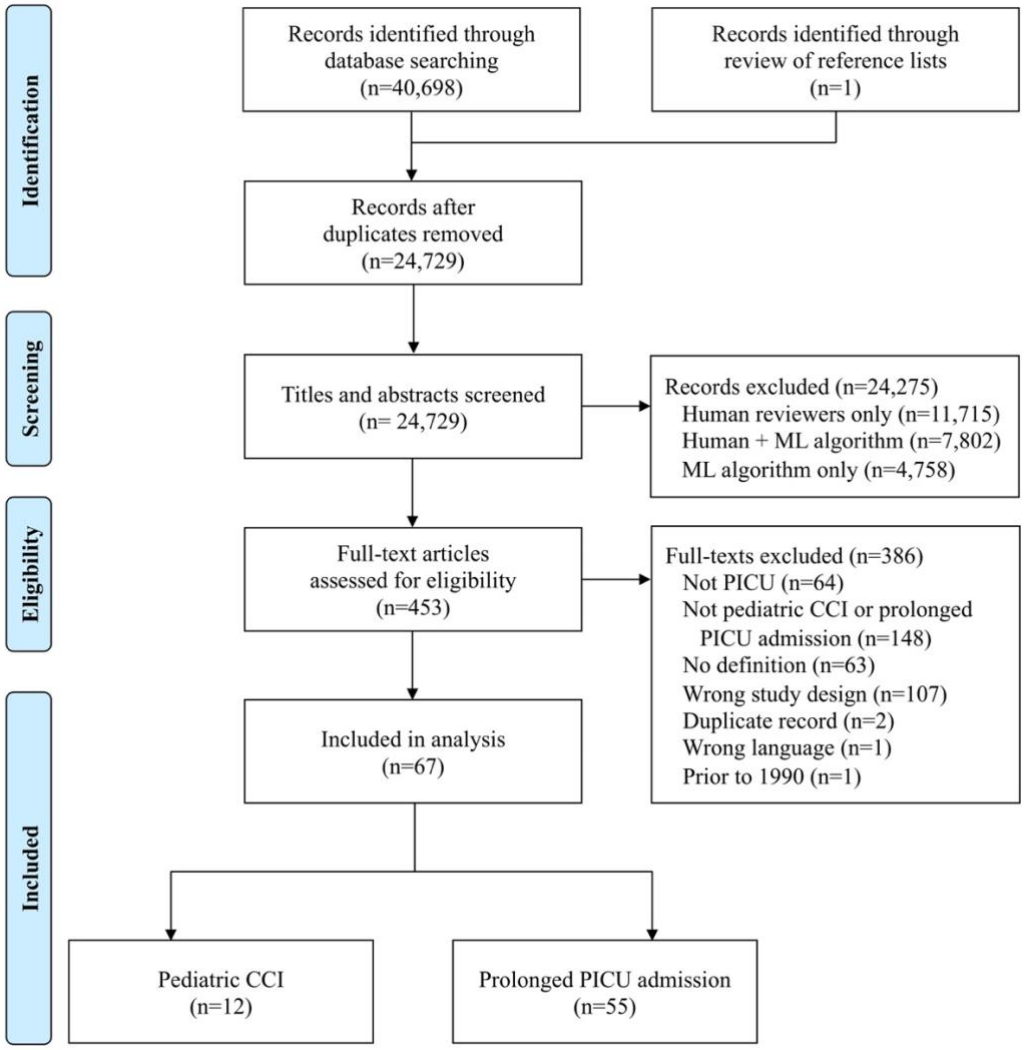


Figure 3. PRISMA flow diagram of study selection[a]. Legend: CCI, chronic critical illness; ML, machine-learning; PICU, pediatric intensive care unit. [a] Combining citations identified in the initial database search and those from review of reference lists

3.4. Study characteristics

We have summarized the characteristics of included studies in **Table 3**. Included studies are predominantly published in English (n=66 studies, 98.5%), and most commonly originating from North America (n=29, 43.3%), Europe (n=16, 23.9%), and Asia (n=11, 16.4%). Included studies were most commonly single-centered (n=40, 59.7%), observational (n=58, 86.6%) and retrospective (n=43, 64.2%). **Figure 4** demonstrates the number of publications per year since

1990 and the cumulative growth in publications on the topics of pediatric CCI or prolonged PICU admission. The majority of publications regarding pediatric CCI or prolonged PICU admission have been published in the last 10-years (n=51 studies, 89.5%). The first study to introduce and specifying a definition for the term "CCI" was published in 2015[16].

Amongst 67 included studies, 12 studies (17.9%) described a definition for children with CCI[16 19 20 23 73 75 78 86 89 91 95 98] and 55 studies (82.1%) studies described a definition for children with prolonged PICU admission[6-8 18 22 24 49-72 74 76 77 79-85 87 88 90 92-94 96 97 99-101].

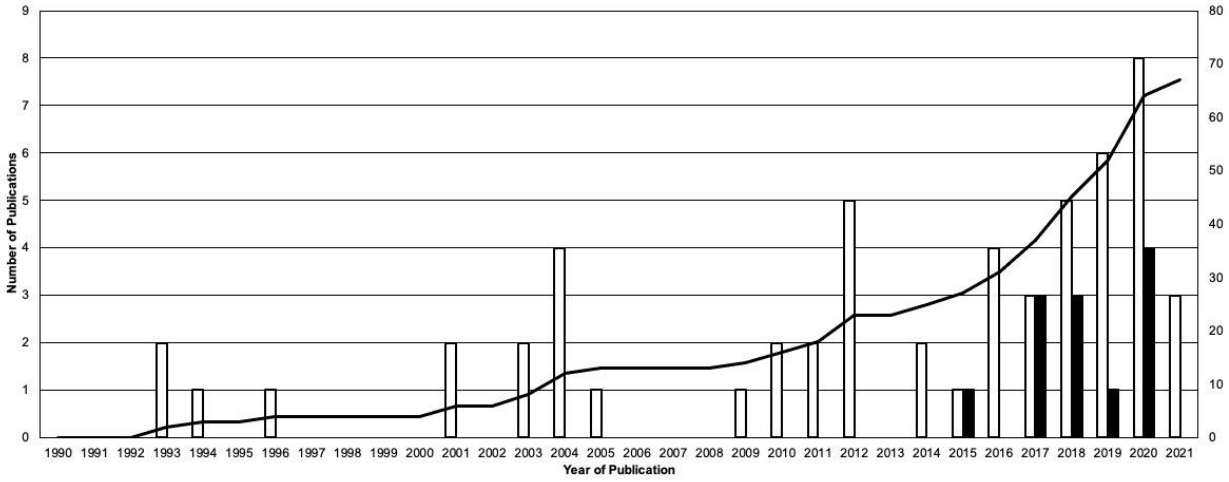


Figure 4. Number of publications over time. Black bars indicate number of studies evaluating pediatric CCI. White bars indicate number of studies evaluating prolonged PICU admission. Black line represents cumulative total studies (secondary axis).

Table 3. Characteristics of included studies

Characteristic	Value
Country, n (%)	
North America	29 (43.2)
Europe	18 (26.9)
Asia	11 (16.4)
Oceania	5 (7.5)
South America	2 (3.0)
Africa	1 (1.5)
Indeterminate	1 (1.5)
Study Design, n (%)	
Observational	58 (86.6)
Qualitative	6 (9.0)
Survey	1 (1.5)
Mixed-methods	1 (1.5)
Protocol	1 (1.5)
Clinical Setting, n (%)	
Number of Centres	
Single	40 (59.7)
Multiple	27 (40.3)
Number of centres, median (Q1, Q3)	8 (6, 32)
Type of Setting(s)	
Unspecified PICU	26 (38.8)
Medical-surgical-cardiac PICU	22 (32.8)
Cardiac only PICU	14 (20.9)
Medical-surgical only PICU	7 (10.4)
Military PICU	1 (1.5)
Other [a]	9 (13.4)
Types of Study Participants, n (%)	
Patients	61 (91.0)
Families	6 (9.0)
Healthcare professionals	11 (16.4)
Other [b]	5 (7.5)

Legend: PICU, pediatric intensive care unit.

[a] Other settings included neonatal intensive care units, general pediatric inpatient wards, outpatient centers, long-term care/rehabilitation centers.

[b] Other study participants were lawyers, non-clinical healthcare administrators, or unspecified.

3.4.1. Definitions of Pediatric "Chronic Critical Illness"

Details of the concepts included in published definitions of pediatric CCI are described in **Table 4**. Of the 12 studies describing a definition for children with "CCI," two studies defined CCI based only on PICU LOS exceeding 14 days[91] or 28 days[16], respectively. The remaining 10 studies defined CCI based on a combination of a prolonged PICU LOS and additional patient characteristics (**Table 4**): recurrent acute care/PICU admissions (n=9), dependence on technology to sustain organ function (n=5), persistent "multiple vital organ system involvement" (n=4), presence of "complex and chronic medical conditions" (n=5), and/or having "uncertain prognosis" (n=1). The threshold for prolonged PICU LOS in these studies was 14 days (n=4), "months" (n=1), or not specified (n=5).

Of the nine studies that included recurrent admissions as a concept in their definition of pediatric CCI, two studies specified ≥2 hospital admissions in 12 months and two studies specified ≥2 acute care/PICU admissions in 12 months. Dependent technologies included in definitions consisted of tracheostomy, invasive and non-invasive mechanical ventilation, gastrostomy or jejunostomy tube, and dialysis[75 86 89 95], but also central lines, intracranial shunts, and history of organ or bone marrow transplant[86]. The most specific description of "multiple organ system involvement" in any definition was, "a chronic medical problem in ≥2 organ systems that has already lasted, or was expected to last, >3 months"[86]. The concept of "complex and chronic medical conditions" in the CCI definitions of five studies was not further specified[19 20 23 78 98].

The definition methodologies for studies of pediatric CCI are summarized in **Table 5**. Most commonly, studies referenced their definition from another source (n=6, 50.0%). Of these, five studies cited their definition from the same source[15], but the reported population definitions

in the methods of two studies were different from the primary source by including: a LOS threshold for total hospital stay[86 89], a LOS threshold for cardiac only PICU patients[89], recurrent unspecified hospitalizations[89], a specific number quantifying "multiple organ system involvement"[86 89], and/or a broader list of organ support technologies to be considered[86]. One study cited a source that did not report any definition for pediatric CCI[106]. The definition of CCI in one study was derived by a statistical method, using a receiver operating curve for the outcome of overall mortality (area under the curve, 0.70; sensitivity, 0.50; specificity, 0.85)[91]. The remaining five studies did not state the rationale for their definition of CCI.

The prevalence of children with CCI in the PICU only was reported in one study, with a prevalence of 1.3%[16]. Two studies reported the prevalence of children with CCI in patient locations beyond the PICU setting, with a prevalence of 36.8%[89] (inclusive of PICU, cardiac PICU, NICU, and inpatient wards) and 40.6%[86] (inpatient wards only), respectively.

Table 4. Definitions of pediatric chronic critical illness

Study (Year)	Concept				Population Prevalence
	Length of Stay	***Hospital Readmission***	***Technology Dependence***	***Medical Complexity & Chronic Conditions***	
Hauschild et al. (2020)[91]	PICU ≥14 days	Not included	Not included	Not included	Indeterminate[a]
Namachivayam et al. (2015)[16]	PICU >28 days	Not included	Not included	Not included	1056/80648 (1.3%)
Boss et al. (2020)[b 89]	NICU >28 days post-term corrected age **or** PICU/CICU >14 days **or** Total stay >180 days	≥2 hospitalizations in past 12 months	**and** "Current medical technology (e.g., mechanical ventilation, feeding tubes, and shunts)"	**or** "Chronic conditions affecting ≥2 organ systems"	385/1046 (36.8%)[c]
Ruth et al. (2020)[b 95] Boss et al. (2018)[b 75]	NICU >28 days post-term corrected age **or** PICU >14 days	≥2 acute care or PICU admissions within 12 months	**and** "Ongoing dependence ≥1 technologies to sustain vital functions (e.g., tracheostomy, invasive or non-invasive mechanical ventilation, gastrostomy or jejunostomy tube, dialysis)"	**or** "Persistent multiple vital organ system involvement"	
Wright-Sexton et al. (2020)[98]	"Prolonged ICU hospitalizations" (unspecified) **and**	"Recurrent ICU hospitalizations" (unspecified) **and**	"Require medical technology for the support of vital functions" **and**	"Complex and chronic medical conditions"	12 total
Rogozinski et al. (2019)[86]	NICU ≥44 weeks' postmenstrual age **or** PICU ≥14 days **or** Hospitalized for >180 days	≥2 hospitalizations in past 12 months	**and** "Ongoing dependence on technology (defined as tracheostomy, mechanical ventilation, any oxygen delivery system, surgical or nonsurgical feeding tubes, indwelling catheters, central lines, dialysis, intracranial shunts, history of organ or bone marrow transplant)"	**or** "Multiple organ system involvement (i.e., a chronic medical problem in ≥2 organ systems that has already lasted, or was expected to last, >3 months)"	232/571 (40.6%)
Donohue et al. (2018)[23]	"Prolonged ICU hospitalizations" (unspecified) **and**	"Recurrent ICU hospitalizations" (unspecified)	Not included **and**	"Complex and chronic medical conditions"	n/a[d]
Seltzer et al. (2018)[e 78] Boss et al. (2017)[e 20]	"Prolonged ICU hospitalizations" (unspecified) **and**	"Recurrent ICU hospitalizations" (unspecified)	Not included **and**	"Complex and chronic medical conditions"	n/a[d]

Henderson et al. (2017)[e 19]					
Shapiro et al. (2017)[73]	"Months in the PICU"	Not included	Not included	***and*** "Uncertain prognosis"	n/a[d]

Legend: CICU, cardiac intensive care unit; ICU, intensive care unit; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit
[a] Study population described as Persistent Inflammation, Immunosuppression, and Catabolism Syndrome in critically ill children (PICS-ped). One component of the PICS-ped definition is "CCI." Study reporting did not permit calculation of prevalence of children classified as having CCI. [b,f] Multiple reports from same data set. [c] Prevalence inclusive of all study settings. Study reporting did not permit calculation of prevalence in individual settings. [d] No patient-level data. [e] Study participants (clinical and non-clinical) recruited from five metropolitan areas: Seattle, WA, Houston, TX, Jackson, MS, Baltimore, MD, and Philadelphia, PA. Clinical settings included, "NICU and PICUs, other inpatient sites, rehabilitation facilities, and outpatient pediatric practices."

Table 5. Pediatric chronic critical illness definition methodologies

Study (Year)	Setting(s)	Study Design	Study Population Definition Concepts				Definition Method
			LOS	***Hospital Readmission***	***Technology Dependence***	***Medical complexity***	
Hauschild et al. (2020)[91]	Medical-surgical PICU	Observational	x				Statistical method (ROC)
Namachivayam et al. (2015)[16]	Medical-surgical-cardiac PICUs	Observational	x				Not stated
Boss et al. (2020)[a 89]	Unspecified PICUs Cardiac only PICUs NICUs Inpatient wards	Observational	x	x	x	x	Cited from another study (Shapiro et al., 2017)[15]
Ruth et al. (2020)[a 95]							
Boss et al. (2018)[a 75]							
Wright-Sexton et al. (2020)[98]	Unspecified PICU	Qualitative	x	x	x	x	Cited from another study (Shapiro et al., 2017)[15]
Rogozinski et al. (2019)[86]	Inpatient wards	Observational	x	x	x	x	Cited from another study (Shapiro et al., 2017)[15]
Donohue et al. (2018)[23]	Metropolitan areas[b]	Qualitative	x	x		x	Not stated
Seltzer et al. (2018)[c 78]	Metropolitan areas[b]	Qualitative	x	x		x	Cited from another study (Seltzer et al., 2015)[106]
Boss et al. (2017)[c 20]							Not stated
Henderson et al. (2017)[c 19]							
Shapiro et al. (2017)[73]	Unspecified PICU NICU	Survey	x			x	Not stated

Legend: LOS, length of stay; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; ROC, receiver operating curve

[a,c] Multiple reports from same data set. [b] Study participants (clinical and non-clinical) recruited from five metropolitan areas: Seattle, WA, Houston, TX, Jackson, MS, Baltimore, MD, and Philadelphia, PA. Clinical settings included, "NICU and PICUs, other inpatient sites, rehabilitation facilities, and outpatient pediatric practices."

3.4.2. Definitions of Prolonged PICU Admission

Fifty-five studies, evaluating a total of 41,449 patient admissions, exclusively described a definition for prolonged, long-stay, or chronic PICU admission (**Table 6**). Prolonged PICU admission was variably defined across all studies with a threshold for PICU LOS ranging from 1 day to 6 weeks. The most common LOS thresholds were 14 days (n=11, 25.4%) or 28 days (n=10, 18.2%). Three studies described two separate LOS thresholds for prolonged PICU admission, which varied based on either patient characteristics (i.e., age or cardiac operative status)[90 92] or type of PICU (i.e., cardiac or non-cardiac PICU)[68]. One study described multiple thresholds for prolonged PICU admission depending on patient age and diagnostic category, ranging from 3.7 to 18.7 days[85]. **Figure 5** illustrates the frequency of LOS thresholds used in included studies to define prolonged PICU admission, categorizing them in 7-day intervals for convenience. The prolonged PICU admission threshold used by included studies over time is depicted in **Figure 6**.

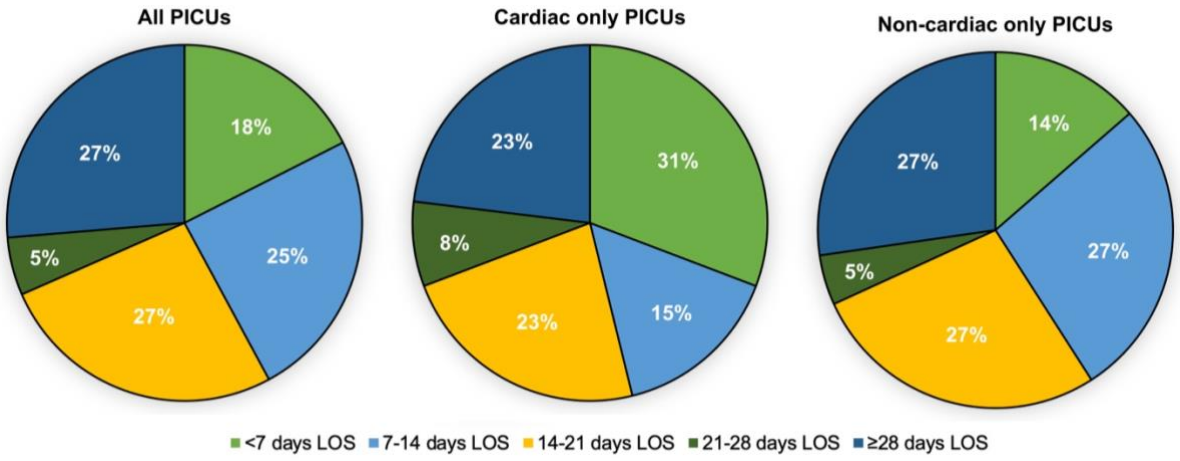


Figure 5. Prolonged PICU admission threshold category by PICU type

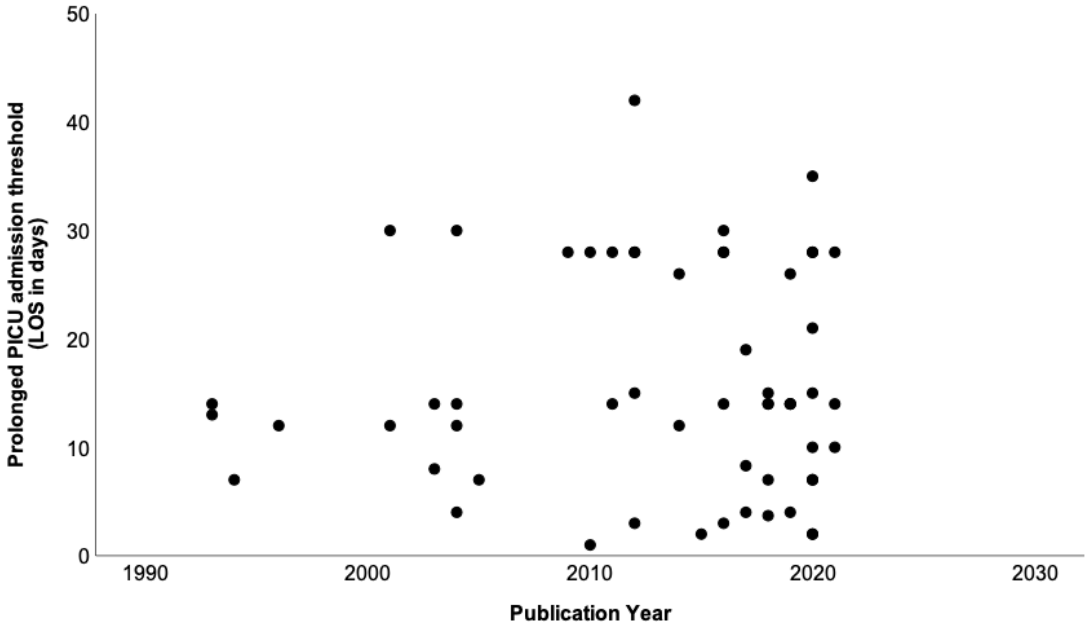


Figure 6. Prolonged PICU admission threshold over time

The rationale for the definition of prolonged PICU admission was described in 31 studies (56.4%), most commonly by statistical method (n=18, 58.1%). The most common statistical method applied was a percentile LOS cut-off for their PICU population (n=15 studies), ranging from the 75th percentile[74] to 97th percentile[57], with variability in the resultant prolonged PICU LOS threshold even when the same percentile was used. Ten studies (18.2%) referenced their prolonged PICU admission threshold from multiple publication(s) which themselves used variable methods to define a threshold for prolonged PICU admission.

The prevalence (median [Q1, Q3]) of children with prolonged PICU admission in these studies was 9.8% (4.4%, 20.6%), ranging from 1.0%[63] to 66.3%[66]. Prevalence by LOS threshold is depicted in **Figure 7**. In contrast to studies evaluating pediatric CCI, studies of children with prolonged PICU admission did not evaluate patient prevalence in settings beyond the PICU. Study reporting did not permit data collection on the number of children with prolonged PICU

admission in four studies[81 85 94 104], one study that was a protocol paper (i.e., no patient data)[83], and one study that only evaluated parents of children with prolonged PICU admission[68].

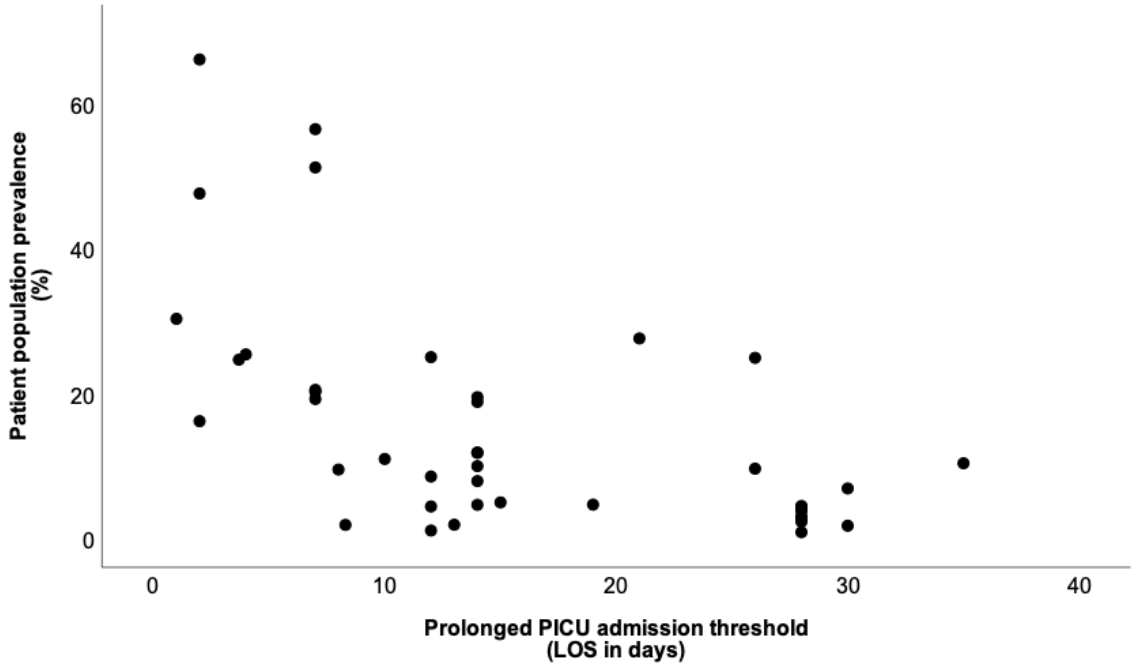


Figure 7. Patient population prevalence by prolonged PICU admission threshold

Table 6. Definitions of prolonged PICU admission

Study (Year)	Setting(s)	Study Design	Definition LOS Threshold	Definition Method	Population Prevalence
Thresholds <7 days LOS					
Spentzas et al. (2010)[58]	Medical-surgical PICU	Observational	1 day	Not stated	32/105 (30.5%)
Beg et al. (2015)[66]	Cardiac only PICU	Observational	2 days	Other[a]	65/98 (66.3%)
Saito et al. (2020)[96]	Unspecified PICU	Observational	2 days	Not stated	8/29 (16.3%)
Karmegaraj et al. (2020)[92]	Cardiac only PICU	Observational	48 hours (pre-operative)	Not stated	66/138 (47.8%)
Levin et al. (2012)[104]	Unspecified PICU	Observational	3 days	Not stated	Indeterminate[b]
Carcillo et al. (2016)[67]	Medical-surgical-cardiac PICU	Observational	3 days	Not stated	254 total
Alam et al. (2018)[74]	Cardiac only PICU	Observational	89 hours	Statistical method (75^{th} percentile)	270/1088 (24.8%)
Sarginson et al. (2004)[55]	Medical-surgical-cardiac PICU	Observational	4 days	Not stated	1241 total
Moynihan et al. (2017)[71]	Cardiac only PICU	Observational	4 days	Statistical method (75^{th} percentile)	444/1737 (25.6%)
Gale et al. (2019)[81]	Military ICUs	Observational	4 days	Cited from another study (Levin et al.)[104]	Indeterminate[b]
Thresholds ≥7 days LOS					
Gemke et al. (1994)[103]	Medical-surgical-cardiac PICU	Observational	7 days	Statistical method ($>80^{th}$ percentile)	115/593 (19.4%)
den Brinker et al. (2005)[56]	Unspecified PICU	Observational	7 days	Not stated	11/54 (20.4%)
Woodger et al. (2018)[79]	Unspecified PICU	Mixed-methods	7 days	Statistical method ($>80^{th}$ percentile)	108/523 (20.6%)
Arafah et al. (2020)[87]	Medical-surgical PICU	Observational	7 days	Not stated	72/127 (56.7%)
Karmegaraj et al. (2020)[92]	Cardiac only PICU	Observational	7 days (post-operative)	Not stated	55/107 (51.4%)
Studdert et al. (2003)[53]	Medical-surgical PICU	Observational	8 days	Statistical method ($>85^{th}$ percentile)	110/1142 (9.6%)
Piastra et al. (2017)[72]	Unspecified PICU	Observational	200 hours	Not stated	7/352 (2.0%)

DeWitt et al. (2020)[90]	Cardiac only PICU	Observational	10 days (non-neonates)	Statistical method (>90th percentile)	1184/10650 (11.1%)
Edwards et al. (2021)[99]	Medical-surgical-cardiac PICU	Observational	10 days	Cited from another study (Gold et al.)[107]	29170 total
Ruttimann et al. (1996)[105]	Unspecified PICU	Observational	12 days	Statistical method (>95th percentile)	222/18432 (1.2%)
Marcin et al. (2001)[18]	Unspecified PICU	Observational	12 days	Statistical method (>95th percentile)	507/11165 (4.5%)
Graham et al. (2004)[54]	Medical-surgical PICU	Observational	12 days	Cited from another study (Marcin et al.)[18]	37/427 (8.7%)
Gil-Ruiz Gil-Esparza et al. (2014)[65]	Medical-surgical-cardiac PICU	Observational	12 days	Cited from another study (Marcin et al.)[18]	103/209 (25.2%)
Kapil et al. (1993)[50]	Unspecified PICU	Observational	13 days	Not stated	61/3025 (2.0%)
Thresholds ≥14 days LOS					
Groeger et al. (1993)[49]	Unspecified PICU	Observational	14 days	Not stated	245/1290 (19.0%)
Brown et al. (2003)[52]	Cardiac only PICU	Observational	14 days	Statistical method (>95th percentile)	41/342 (12.0%)
Briassoulis et al. (2004)[6]	Unspecified PICU	Observational	14 days	Not stated	320/1629 (19.6%)
Pagowska-Klimek et al. (2011)[60]	Cardiac only PICU	Observational	14 days	Statistical method (>90th percentile)	70/692 (10.1%)
Geoghegan et al. (2016)[68]	Cardiac only PICU	Qualitative	14 days	Other[c]	n/a[d]
Eveleens et al. (2018)[80]	Medical-surgical-cardiac PICU	Observational	14 days	Not stated	70 total
Ping Kirk et al. (2018)[77]	Medical-surgical-cardiac PICU	Observational	14 days	Not stated	241/5069 (4.8%)
Knaup et al. (2019)[82]	Medical-surgical-cardiac PICU	Observational	14 days	Statistical method[e]	330/4107 (8.0%)
Madrigal et al. (2019)[83]	Unspecified PICU	Protocol	14 days	Not stated	n/a[d]
Matsumoto et al. (2019)[84]	Medical-surgical-cardiac PICU	Observational	14 days	Not stated	111 total
Ehinger et al. (2021)[100]	Unspecified PICU	Observational	14 days	Not stated	291/2434 (12.0%)

Edwards et al. (2012)[61]	Unspecified PICU	Observational	15 days	Statistical method (>95th percentile)	2688/52791 (5.1%)
Madden et al. (2018)[76]	Medical-surgical PICU	Observational	15 days	Not stated	88 total
O'Keefe et al. (2020)[94]	Unspecified PICU	Observational	15 days	Cited from another study (Lutmer et al.)[108]	Indeterminate[b]
Nupen et al. (2017)[70]	Medical-surgical-cardiac PICU	Observational	19 days	Statistical method (>95th percentile)	54/1126 (4.8%)
Thresholds ≥21 days LOS					
Temsah et al. (2020)[97]	Medical-surgical-cardiac PICU	Observational	21 days	Not stated	83/299 (27.8%)
Baker-Smith et al. (2014)[64]	Cardiac only PICU	Observational	26 days	Statistical method (>75th percentile)	76/303 (25.1%)
Arias Lopez et al. (2019)[88]	Medical-surgical-cardiac PICU	Observational	26 days	Statistical method (>90th percentile)	340/3483 (9.8%)
Thresholds ≥28 days LOS					
Conlon et al. (2009)[57]	Medical-surgical-cardiac PICU	Observational	28 days	Statistical method (>97th percentile)	193/6179 (3.1%)
Naghib et al. (2010)[7]	Medical-surgical-cardiac PICU	Observational	28 days	Statistical method (3x median LOS)	116/2607 (4.4%)
Gonzalez-Cortes et al. (2011)[59]	Medical-surgical-cardiac PICU	Observational	28 days	Not stated	83/2118 (3.9%)
Namachivayam et al. (2012)[22]	Medical-surgical-cardiac PICU	Observational	28 days	Cited from another study (ANZPIC Registry report, 2009)	233 total
Straney et al. (2012)[63]	Unspecified PICU	Observational	28 days	Not stated	125/12763 (1.0%)
Geoghegan et al. (2016)[68]	Medical-surgical PICU	Qualitative	28 days	Other[c]	n/a[d]
Namachivayam et al. (2016)[69]	Medical-surgical-cardiac PICU	Observational	28 days	Not stated	116 total
Kanthimathinathan et al. (2020)[8]	Medical-surgical-cardiac PICU	Observational	28 days	Cited from another study (multiple)[7 22 59]	705/24203 (2.9%)
Miura et al. (2020)[93]	Medical-surgical-cardiac PICU	Observational	28 days	Cited from another study (multiple)[7 22 59]	32/1309 (2.4%)
Garcia Mancebo et al. (2021)[101]	Medical-surgical-cardiac PICU	Observational	28 days	Cited from another study (Gonzalez-Cortes et al.)[59]	179/3881 (4.6%)
Auburtin et al. (2001)[51]	Medical-surgical PICU	Observational	30 days	Statistical method (>95th percentile)	95 total

van der Heide et al. (2004)[24]	Unspecified PICU	Observational	30 days	Not stated	19/1015 (1.9%)
Mori et al. (2016)[102]	Cardiac only PICU	Observational	30 days	Other[f]	108/1538 (7.0%)
DeWitt et al. (2020)[90]	Cardiac only PICU	Observational	35 days (neonates)	Statistical method (>90th percentile)	242/2312 (10.5%)
Garcia et al. (2012)[62]	Cardiac only PICU	Observational	6 weeks	Not stated	68 total
Other LOS Thresholds					
Polito et al. (2019)[85]	Medical-surgical-cardiac PICU	Observational	Variable definition per age and diagnostic category (range 3.7-18.7 days)	Statistical method (>90th percentile)	Indeterminate[b]
DeWitt et al. (2020)[90]	Cardiac only PICU	Observational	70 days (neonates) 20 days (non-neonates) ("ultra-long stay")	Statistical method (>99.5th percentile)	121/2312 (5.2%)
Briassoulis et al. (2004)[6]	Unspecified PICU	Observational	90 days ("very prolonged")	Not stated	11/1629 (0.7%)

Legend: CICU, cardiac intensive care unit; ICU, intensive care unit; LOS, length of stay; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; ROC, receiver operating curve.

[a] Threshold used was median LOS post-Tetralogy of Fallot repair cited from literature. [b] Study reporting did not permit calculation of prevalence. [c] Threshold selected based on institutional definitions. [d] No patient-level data. [e] Threshold selected based on results of three statistical methods: five times median LOS, 95th percentile, and the start of the "tail" of the LOS plot distribution. [f] Threshold selected based on "the definition of chronic critical illness."

CHAPTER IV: DISCUSSION & CONCLUSIONS

4.1. Discussion

The results of this scoping review of published studies evaluating either pediatric CCI or prolonged PICU admission, demonstrated the following key findings: First, there are no published consensus definitions for either pediatric CCI or prolonged PICU admission. Operational definitions in the literature of CCI and what constitutes a prolonged PICU admission have been derived in a variety of ways, most commonly by investigator opinion. Second, the term "pediatric CCI" is defined variably in the literature; most frequently, it is anchored upon concepts of prolonged PICU LOS, patient medical complexity, patient technology-dependence, and recurrent admissions. However, the way these concepts are specified in definitions are both variable and often subjective. What constitutes a prolonged PICU admission is also variably defined, but most commonly referred to either ≥14 days or ≥28 days LOS (depending on population studied). Third, we observed significant heterogeneity in the reported prevalence of children with either pediatric CCI or prolonged PICU admission, based on reported definitions. Finally, this scoping review demonstrates the feasibility of executing a large review enhanced by a hybrid crowdsourcing and ML algorithm citation screening methodology.

Since the introduction of the concept in 2015, 12 included studies have used the term "CCI" in children and definitions were mostly derived by investigator opinion or referenced from another study. These studies often traced their population definition to a narrative review by Shapiro et al.[15] describing an expert opinion-based definition of pediatric CCI, with the reported definition being modified in subsequent studies. In contrast, studies focused on children with prolonged PICU admission are more frequent. The "long-stay" PICU patient was first described in the literature by Pollack et al.[109] in 1987, using a threshold of 13 days (>95th

percentile LOS). Over the next three decades, we observed that studies have evaluated 41,449 prolonged PICU admissions, yet there remains considerable variability in the definition of a prolonged PICU admission even amongst studies that used the same statistical threshold as Pollack et al. (range 12 days[18] to 30 days[51]). Many studies included in this review (n=24, 43.6%) also did not state the rationale for their prolonged LOS threshold, and of those that did, their methodologies were heterogeneous. As such, this scoping review demonstrates that there remains significant heterogeneity in the definitions of pediatric CCI and the concept of prolonged PICU admission, heralding a lack of (and need for) consensus in order to systematically evaluate this population in future studies.

Predictably, we also observed that the prevalence of children with CCI or prolonged PICU admission was highly variable in included studies based on their stated definitions. While this observation may reflect the inconsistency in definitions used, it may also be resultant of patient or PICU characteristics. Some studies included in this review suggest that thresholds for prolonged PICU admission may depend on patient setting (i.e., cardiac only PICUs), age, or underlying disease state[68 85 90 92]. Patient prevalence in studies of pediatric CCI specifically was also difficult to interpret, as only one study (defining CCI by only a PICU LOS) reported prevalence within the PICU setting only[16]. However, studies measuring pediatric CCI beyond the PICU suggest that these patients are broadly prevalent in a variety of non-acute settings, underscoring the need to understand this patient population more precisely. The observed variability in prevalence of children with defined prolonged PICU admission—regardless of the threshold chosen—may also indicate that this concept alone is insufficient to define pediatric CCI. A unifying definition for pediatric CCI may require additional concepts to address the heterogeneity and potential imprecision of a definition based solely on PICU LOS.

The results of our scoping review have highlighted potential additional concepts to consider when defining pediatric CCI. These additional concepts may be necessary to reflect the evolution of pediatric critical care, our ability to provide advanced organ support technologies beyond the PICU, and the increasing recognition of our patient's chronic morbidities that may put them at-risk for CCI[1 3 9 11 110]. The association between patient medical complexity and prolonged PICU admission has been previously described[6 18 22 24 61], leading to the hypothesis that children with CCI may be a subset of those with medical complexity who have prolonged reliance on critical care supports and worse outcomes. As demonstrated in this scoping review, definitions of CCI have often subjectively operationalized the concept of "medical complexity," and future planned analyses of this review will explore how medical complexity and chronic comorbidities have been measured in the current literature as a way to inform how to best to incorporate this concept in a consensus case definition of CCI.

Proposed definitions of pediatric CCI have also included the concept of "technology-dependence"[75 86 89 95 98]. It has been suggested that prolonged non-invasive or invasive mechanical ventilation is a requisite feature of children with CCI[111]; however, studies included in this review did not consistently identify what organ support technologies should be considered in a definition of pediatric CCI, nor if an amount or duration of support is a modifying factor. Children with feeding and respiratory technology dependence have a heavy reliance on PICU therapies and longer lengths of stay, but not all have higher morbidity rates when compared to children without technology dependence[112]. There are also many children who are supported by some of technologies listed in current definitions (e.g., dialysis, central lines, feeding tubes) that do not require prolonged PICU admissions. Future planned analyses from this scoping review will seek to explore the technologies studied and identified in children with CCI and prolonged

PICU admission, to help inform how this concept may be integrated into a unifying definition of pediatric CCI.

Finally, some definitions of pediatric CCI included repeated PICU admissions as an indicator of CCI[19 20 23 75 78 86 89 95 98], supported by several studies describing poor outcomes in children with frequent PICU admissions[11 113 114]. Again, this concept was often subjectively described in definitions, and even studies elaborating on this concept demonstrated variability (i.e., considering acute care versus non-acute care readmissions). It remains unclear if repeated admissions are an outcome rather than an indicator of CCI, as frequent readmissions are associated with patients with medical complexity[11 113 114]. In future analyses, we plan to describe how often patient readmission has been measured in studies included in this scoping review.

4.2. Strengths and limitations

To our knowledge, this scoping review is the first evidence synthesis to provide a systematic overview of the definitions used in the literature to identify children with CCI and prolonged PICU admission. As such, this review has emphasized that a consensus process is needed to advance the field of pediatric CCI research. Second, we have successfully incorporated two innovative evidence synthesis methods—crowdsourcing and an ML algorithm—in order to execute a large scoping review in an efficient timeline without hindering sensitivity. We used targeted recruitment techniques to assemble a curated, multinational and multidisciplinary crowd with a performance (i.e., sensitivity, 92.1%) consistent with or better than other studies evaluating the sensitivity of single and crowdsourced reviewers[33 36 45 46]. A rigorous data-driven approach was used to conservatively integrate an ML algorithm into citation screening, which missed none of the included studies and significantly improved review efficiency (17,370

duplicate citation assessments saved). Our protocol was designed and published a priori in pre-print. Finally, this scoping review created a high-performance collaboration with a global outreach, demonstrating that crowdsourcing may be a feasible strategy to improve the nature and extent of research collaborations in future PICU research.

This review also has important limitations. As the goal of this scoping review was to describe definitions of pediatric CCI and prolonged PICU admission, it is limited to studies that explicitly identified and defined these concepts. This review will have potentially missed records that did not use this specific language to define their population, and excluded studies that did not provide or reference a definition of pediatric CCI or prolonged PICU admission. As such, the results may underestimate the total extent of literature in this field to date. Similarly, this review also excluded studies that focussed on the concept of any prolonged technology use (e.g., prolonged mechanical ventilation, prolonged extracorporeal membrane oxygenation). We sought to broadly understand pediatric CCI, and the results of this review demonstrate that there is no consensus regarding pre-requisites for a specific organ support technology in the current published definitions of pediatric CCI. In keeping with a scoping review methodology, we did not evaluate individual study risk of bias or certainty of evidence.

4.3. Knowledge-translation and dissemination plan

The final results of this scoping review will be published in a peer-reviewed journal and disseminated to key stakeholders (e.g., PICU clinicians, complex care pediatricians, research funders and the public) through presentations at national and international conferences, and social media (Twitter) using investigators' accounts and content-specific hashtags (i.e., #PedsICU, #PICSp, #CCI). Team members will also disseminate the results through relevant

research groups, including the Canadian Critical Care Trials Group (Canada) and the Pediatric Acute Lung Injury and Sepsis Investigators group (United States). Dissemination and incorporation of the results of this scoping review will also be facilitated by a future survey of clinicians and a Delphi process to develop a consensus definition for pediatric CCI.

4.4. Future directions

This report is a preliminary analysis of the results of a large scoping review on pediatric CCI. Further analyses will focus on the secondary aims of this scoping review, describing the demographics and clinical characteristics in children with CCI in the current literature. Future planned analyses will also describe the types of outcomes evaluated in included studies, including child-, family-, provider-, and system-based outcomes. This scoping review is the first phase of a larger program of research to systematically evaluated children with CCI. The results of this review will be used to inform the development of a consensus case definition for pediatric CCI and set a priority agenda for future research. Defining pediatric CCI is an essential first step to understanding the epidemiology of this high-risk PICU population, and a pre-requisite for conducting future interventional and outcomes research.

A survey study is planned with the objective of describing Canadian clinicians' knowledge and perceptions of post-PICU morbidities in children (including concepts of post-intensive care syndrome and CCI) and current practice patterns of post-PICU follow-up. Canadian clinicians' knowledge and perceptions of PICS-p and the survivorship of critically ill children has yet to be evaluated. In order to improve the quality of PICU care provided—targeted towards enhancing survivorship—it is imperative that clinicians understand the implications of the post-intensive care syndrome. As a starting point, we will evaluate this knowledge gap by

assessing the current awareness of the common and growing problem of post-PICU morbidities in Canada.

4.5. Conclusions

This scoping review has highlighted that definitions of pediatric CCI in the current literature, while variable and often subjective, prompt the examination of including additional concepts (i.e., patient medical complexity, technology-dependence) addressing complexity in addition to chronicity (i.e., prolonged PICU LOS, hospital readmission) to more precisely define this patient population. Similarly, the concept of prolonged PICU admission has also been heterogeneously defined, despite several studies spanning over three decades. As a result, this scoping review has justified the need for a future consensus process to create a unifying definition of pediatric CCI. Finally, we have demonstrated that a hybrid crowdsourcing and ML methodology can be used to conduct a large scoping review within an extremely efficient timeline without hindering the research objective or citation assessment sensitivity.

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Appendix A. PRISMA-ScR protocol reporting checklist

Section/Topic	Checklist Item	Page Number
Administrative Information		
Title		
Identification	Scoping review title	See online protocol
Authors		
Contact	Provide name, ORCID, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	See online protocol
Contributions	Describe contributions of protocol authors and identify the guarantor of the review	See online protocol
Amendments	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page 6
Introduction		
Rationale	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Pages 2-3
Objectives	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Pages 4-5
Methods		
Protocol and Registration	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Page 6
Eligibility criteria	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Pages 6-7
Information sources	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	Page 7
Search strategy	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 8 Table 1
Selection of sources of evidence	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Pages 9-12

Data charting process	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 13
Data items	List and define all variables for which data will be sought any assumptions and simplifications made.	Page 15 Table 2
Critical appraisal of individual sources of evidence	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Pages 13-14
Summary measures	Not applicable for scoping reviews.	Pages 13-14
Synthesis of results	Describe the methods of handling and summarizing the data that were charted.	Pages 13-14
Risk of bias across studies	Not applicable for scoping reviews.	Pages 13-14
Additional analyses	Not applicable for scoping reviews.	Pages 13-14
Funding		
Sources	Indicate sources of financial or other support for the review	Page 16
Sponsor	Provide name for the review funder and/or sponsor	
Role of sponsor/ funder	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 16

Appendix B. Software platforms and applications

Software	Purpose	Use in Scoping Review
insightScope (www.insightscope.ca)	Web-based platform for performing large literature by crowdsourcing	• Assessing potential crowd reviewer screening sensitivity (i.e., test set administration) • Citation screening (title/abstract, full text) via crowdsourcing • Data abstraction via crowdsourcing
Twitter	Social media communication platform	• Scoping review promotion • Crowd recruitment • Scoping review progress updates • Celebrating review successes
Slack (Slack Technologies, San Francisco, CA)	Cloud-based team communication platform	• Foster "team" environment • Communications between crowd reviewers and core investigator team/study lead • Scoping review progress updates
SourceForge Plot Digitizer (http://plotdigitizer.sourceforge.net)	Digitize scanned plots of functional data	• Data abstraction of graphical data (where necessary)

Appendix C. Search strategy output

a) OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (March 3, 2021)

1. intensive care units/ and (child* or pediatric or paediatric).mp. (3939)
2. Intensive Care Units, Pediatric/ (8176)
3. PICU.mp. (5009)
4. ((p?ediatric* or child or children*) adj3 (acute* or critical* or intens*)).mp. (48211)
5. or/1-4 (51938)
6. exp Critical Care/ (59805)
7. Critical Illness/ (31096)
8. (critical* or intens*).mp. (1720561)
9. or/6-8 (1720588)
10. exp Chronic Disease/ (267032)
11. "Length of Stay"/ (91841)
12. ((long or duration or length) adj3 (stay or hospitali*)).mp. (158054)
13. or/10-12 (423118)
14. 5 and 9 and 13 (3278)
15. ((chronic* or persist* or long term or longterm or long-stay or prolong* or protract* or extend* or extensive or lengthy or difficult*) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. (263664)
16. 5 and 15 (2499)
17. 14 or 16 (5466)
18. ((p?ediatric* or child or children*) adj5 (chronic* or persist* or long term or longterm or prolong* or protract* or extend* or extensive or lengthy or difficult* or ((long or duration) adj3 stay)) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. (6213)
19. 17 or 18 (10569)

b) EMBASE (March 2, 2021)

1. intensive care unit/ and (child* or pediatric or paediatric).mp. (21504)
2. pediatric intensive care unit/ (7327)
3. PICU.mp. (11247)
4. ((p?ediatric* or child or children*) adj3 (acute* or critical* or intens*)).mp. (68212)
5. or/1-4 (84908)
6. exp intensive care/ (734985)
7. critical illness/ (31166)
8. (critical* or intens*).mp. (2275093)
9. or/6-8 (2753604)
10. exp chronic disease/ (186218)
11. "length of stay"/ (203206)
12. ((long or duration or length) adj3 (stay or hospitali*)).mp. (270099)
13. or/10-12 (454302)
14. 5 and 9 and 13 (7657)
15. ((chronic* or persist* or long term or longterm or long-stay or prolong* or protract* or extend* or extensive or lengthy or difficult*) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. (450253)

16. 5 and 15 (4685)
17. 14 or 16 (11688)
18. ((p?ediatric* or child or children*) adj5 (chronic* or persist* or long term or longterm or prolong* or protract* or extend* or extensive or lengthy or difficult* or ((long or duration) adj3 stay)) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. (8638)
19. 17 or 18 (18621)

c) CINAHL (March 2, 2021)

1. MH "Intensive Care Units" (40,153)
2. TX child* or pediatric or paediatric (1,394,611)
3. 1 and 2 (4,163)
4. MH "Intensive Care Units, Pediatric" (6,383)
5. TX PICU (3,711)
6. TX ((p?ediatric* or child or children*) N3 (acute* or critical* or intens*)) (18,904)
7. 3 or 4 or 5 or 6 (27,288)
8. MH "Critical Care+" (29,841)
9. MH "Critical Illness" (13,144)
10. TX (critical* or intens*) (541,631)
11. 8 or 9 or 10 (542,573)
12. MH "Chronic Disease" (65,506)
13. MH "Length of Stay" (44,304)
14. TX ((long or duration or length) N3 (stay or hospitali*)) (67,901)
15. 12 or 13 or 14 (132,722)
16. 7 and 11 and 15 (2,501)
17. (chronic* or persist* or long term or longterm or long-stay or prolong* or protract* or extend* or extensive or lengthy or difficult*) N5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care) (109,352)
18. 7 and 17 (1,289)
19. 16 or 18 (3,501)
20. TX ((p?ediatric* or child or children*) N5 (chronic* or persist* or long term or longterm or prolong* or protract* or extend* or extensive or lengthy or difficult* or ((long or duration) N3 stay)) N5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)) (3,727)
21. 19 or 20 (6,756)

d) Web of Science (March 3, 2021)

1. TS=PICU (5,004)
2. TS=((p?ediatric* or child or children*) NEAR/3 (acute* or critical* or intens*)) (38,585)
3. 1 or 2 (41,705)
4. TS=(critical* or intens*) (3,485,771)
5. TS=(chronic disease) (567,032)
6. TS=((long or duration or length) NEAR/3 (stay or hospitali*)) (117,205)
7. 5 or 6 (679,034)
8. 3 and 4 and 7 (1,932)

9. TI=(chronic* or persist* or long term or longterm or long-stay or prolong* or protract* or extend* or extensive or lengthy or difficult*) (1,174,553)
10. TI=(acute* or critical* or intens* or ill or illness* or sick or sickness* or care) (1,595,757)
11. 9 and 10 (82,128)
12. 3 and 11 (822)
13. 8 or 12 (2,665)
14. TI=(p?ediatric* or child or children*) (790,130)
15. TI=(chronic* or persist* or long term or longterm or prolong* or protract* or extend* or extensive or lengthy or difficult* or ((long or duration) NEAR/3 stay)) (1,175,468)
16. 10 and 14 and 15) (2,756)
17. 13 or 16 (4,752)