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RISK FACTORS AND OUTCOMES OF ONCOHEMATOLOGIC PATIENTS ADMITTED TO PEDIATRIC INTENSIVE CARE UNIT: ONCOTIPNET, AN ITALIAN MULTICENTER STUDY

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ABSTRACT

Background: In the past decades, important progresses have been made in pediatric oncology thanks to a deep understanding of cancer biology that allowed improving patients' survival and ameliorating their outcomes through the implementation of optimized treatment protocols. However, children with cancer still develop serious complications related either to their disease or to its treatment and may require intensive care. Thus, pediatric oncologic patients and particularly those who also undergo allogeneic hematopoietic stem cell transplantation during their treatment course are to be considered as a high-risk population for intensive care needs. The most common causes for pediatric intensive care unit (PICU) admission in these patients are respiratory and neurological complications, as well as sepsis and multiorgan failure. PICU treatments include respiratory support with invasive and non-invasive ventilation, renal replacement therapy, total parenteral nutrition and eventually extracorporeal membrane oxygenation. Despite various scores have been historically developed to assess the severity of patients' clinical conditions during their hospitalization, evaluate the actual need for PICU admission and predict mortality, recent and robust studies regarding PICU admitted oncologic children are lacking in the literature.

Aim of the study: Our study is aimed at describing the pediatric oncologic population admitted to different Italian PICUs with regard to pre-PICU admission variables and during PICU stay variables. Our secondary endpoint is to identify risk factors associated with PICU mortality and length of PICU stay.

Materials and methods: This work is a multicenter retrospective and prospective study involving 14 Italian PICUs. Data were collected from a total of 538 patients admitted to 14 Italian PICUs between January 2019 and April 2022. The retrospective phase involved 239 patients, the prospective phase 299 patients. the data collected include before PICU admission variables and during PICU stay variables. These variables were analysed to describe the overall population of the study, the subpopulations of patients with solid tumor compared to children affected by an hematological neoplasm, and the subpopulations of children who underwent stem cell transplant compared to non-transplanted children. Univariate and

multivariate analyses were performed to identify pre PICU admission and PICU stay risk factors for mortality outcome and for length of PICU stay outcome.

Results: The 54% of the 538 study patients were males. Median age was 7 years (IRQ 2-12). The underlying diagnoses were: solid tumor (51%), acute lymphoblastic leukemia (23%), acute myeloid leukemia (6.2%), non-Hodgkin lymphoma (3.8%), Hodgkin lymphoma (6.1%), others (15%). 19% of the patients underwent HSCT. The most common admission causes were respiratory failure (32%) and neurological deficits (23%). Mortality in PICU was 13%. 428 patients were included in the analysis of risk factors for mortality in PICU and PICU length of stay (patients admitted after surgery who stayed in PICU less than 48 hours were excluded). The multivariate analysis for risk factors associated with mortality outcome showed significant values for the following pre-PICU admission predictors: HSCT (Hematopoietic Stem Cell Transplantation) ($p=0.013$), O-PEWS (Oncological Pediatric Early Warning Score) ($p=0.010$), PIM (Pediatric Index of Mortality) 3 score ($p<0.001$) and priority level (severity of illness) ($p=0.012$); PICU stay predictors: multiorgan failure ($p=0.004$) and cardiac arrest ($p<0.001$). The multivariate analysis for risk factors associated with length of PICU stay showed significant values for multiorgan failure ($p=0.049$) as before PICU admission predictor; PICU stay predictors: invasive and/or non-invasive ventilation length ($p<0.001$) and TPN ($p=0.004$).

Conclusions: Our study reports a lower mortality for pediatric oncologic patients admitted to PICU compared to literature. Early recognition of patients at higher risk, appropriate PICU admission timing and ideal intensive care treatment may further improve patients' outcomes. O-PEWS and PIM 3 score represent important tools to assess patient's severity of illness and have a predictive value on mortality outcome. Up to date guidelines regarding PICU admission criteria, appropriacy and timing of intensive care treatment are needed to ensure the best interdisciplinary approach and to ultimately increase survival rates.

RIASSUNTO

Presupposti dello studio: Negli ultimi decenni sono stati fatti grandi progressi nell'ambito dell'oncologia pediatrica grazie a una conoscenza più profonda della biologia del cancro, che ha permesso di migliorare l'outcome dei pazienti attraverso protocolli di cura ottimizzati. Tuttavia i bambini con tumore possono sviluppare gravi complicanze legate alla malattia di base e ai trattamenti oncologici e possono necessitare di cure intensivistiche. Perciò i bambini con patologie tumorali e in particolare quelli sottoposti a trapianto di cellule staminali ematopoietiche sono una popolazione che presenta alto rischio di ricovero in terapia intensiva. Le principali cause di ricovero in terapia intensiva pediatrica (TIP) per questi pazienti sono l'insufficienza respiratoria, insufficienza multiorgano, deficit neurologici e sepsi. I trattamenti effettuati in terapia intensiva includono anche supporto respiratorio con ventilazione invasiva e non invasiva, dialisi, nutrizione parenterale totale e ossigenazione extracorporea a membrana. Nonostante vari score siano stati sviluppati per valutare la gravità dei pazienti, determinare la necessità di ricovero in TIP e per predire la mortalità, in letteratura non ci sono studi recenti e robusti sul ricovero in terapia intensiva pediatrica di bambini affetti da tumore.

Scopo dello studio: L'obbiettivo primario del nostro studio è descrivere la popolazione di bambini affetti da tumore ricoverati nelle terapie intensive italiane considerando le variabili legate al periodo antecedente al ricovero in TIP e al ricovero in TIP stesso. L'obbiettivo secondario è identificare i fattori di rischio associati alla mortalità e alla durata di degenza.

Materiali e metodi: Questo lavoro è uno studio multicentrico a cui hanno partecipato 14 terapie intensive pediatriche italiane, costituito da una parte retrospettiva e da una parte prospettica. Nello studio sono stati inclusi 538 pazienti ricoverati in terapia intensiva pediatrica tra gennaio 2019 e aprile 2022. La fase retrospettiva ha coinvolto 239 pazienti, mentre la prospettica 299. I dati registrati riguardano sia variabili relative alla fase precedente al ricovero in terapia intensiva che al ricovero in TIP stesso. Nel nostro lavoro sono state analizzate la popolazione generale dello studio, la popolazione di pazienti con tumore solido in rapporto a quella di pazienti con tumore ematologico e la popolazione di bambini trapiantati in rapporto ai bambini non trapiantati. I fattori di rischio per mortalità e durata di

degenza relativi al pre-ricovero in TIP e alla degenza in TIP sono stati analizzati mediante analisi univariate e multivariate.

Risultati: Tra i 538 pazienti inclusi nello studio il 54% erano maschi. L'età media è stata 7 anni (IRQ 2-12). Le diagnosi di malattia di base sono state le seguenti: tumore solido (51%), leucemia linfoblastica acuta (23%), leucemia mieloide acuta (6.2%), linfoma non Hodgkin (3.8%), linfoma di Hodgkin (6.1%), altro (15%). Il 19% dei pazienti erano stati sottoposti a trapianto di midollo. Le cause principali di ricovero sono state complicanze respiratorie (32%) e neurologiche (23%). La mortalità in terapia intensiva pediatrica è stata del 13%. 428 pazienti sono stati inclusi nelle analisi dei fattori di rischio per la mortalità in TIP e per la durata di degenza in TIP. Dall'analisi multivariata della mortalità sono risultate significative in pre-ricovero le seguenti variabili: HSCT (Hematopoietic Stem Cell Transplantation) ($p=0.013$), O-PEWS (Oncological Pediatric Early Warning Score) ($p=0.010$), PIM (Pediatric Index of Mortality) 3 score ($p<0.001$) and priorità ($p=0.012$); durante il ricovero le variabili: insufficienza multiorgano ($p=0.004$) e episodio di arresto cardiaco ($p<0.001$). Dall'analisi multivariata sulla durata della degenza in TIP è risultata significativa in pre-ricovero in TIP la variabile insufficienza multiorgano ($p=0.049$); durante la degenza le variabili: durata della ventilazione invasiva e/o non invasiva ($p<0.001$) e la presenza di NPT ($p=0.004$).

Conclusioni: Il nostro studio riporta una minor mortalità dei pazienti pediatrici oncologici ricoverati in terapia intensiva rispetto agli studi presenti in letteratura. Il riconoscimento precoce dei pazienti a più alto rischio, un'appropriata tempistica nel ricovero in TIP ed un'adeguata terapia potrebbero migliorare ancora di più la sopravvivenza dei pazienti. Il O-PEWS e lo score PIM 3 sono importanti strumenti per determinare la gravità del paziente. Hanno inoltre significato predittivo per la mortalità. Sarebbero tuttavia necessari nuovi aggiornamenti delle linee guida riguardo i criteri di ricovero in TIP, l'appropriatezza e le tempistiche del supporto intensivo in modo da poter assicurare il miglior approccio interdisciplinare e, di conseguenza, migliorare la sopravvivenza.

1. INTRODUCTION

In recent years, remarkable progresses have been made in the field of oncology resulting in significantly improved survival rates for pediatric patients diagnosed with cancer. These advancements can be attributed to the emergence of new therapeutic strategies and targeted therapies, as well as significant improvements in the provision of supportive care and hematopoietic stem cell transplantation (HSCT). These developments collectively contribute to enhanced outcomes for children facing a cancer diagnosis [(1)].

Nevertheless, pediatric oncologic patients may develop severe complications, either as a consequence of their underlying disease or due to the treatment they receive. In such cases, children may require admission to a Pediatric Intensive Care Unit (PICU) to receive the specialized and intensive care and treatment they need.

1.1 Epidemiology of childhood cancer

Despite its relatively low incidence in comparison to other diseases, cancer remains one of the leading causes of mortality among children worldwide. In Europe, cancer ranks as the primary cause of death by disease for children aged 1-14 years and stand as the second most common cause of death overall, second only to external causes, which encompass accidents and injuries[(2)].

Every year, approximately 400,000 children between the ages of 0 and 19 worldwide are diagnosed with cancer[(3)]. Notably, 90% of cases occur in low- and middle-income countries (LMIC), where healthcare systems are often not prepared to manage the disease burden. Consequently, children with cancer in LMIC frequently go undiagnosed and untreated[(4),(5)]. In 2019, an estimated 100,000 children died of cancer[(6).] While there have been significant progresses in improving survival rates in high-income countries (HIC), with rates surpassing 80%, mortality rates in LMIC have either remained stagnant or, in some instances, increased (Figure I).

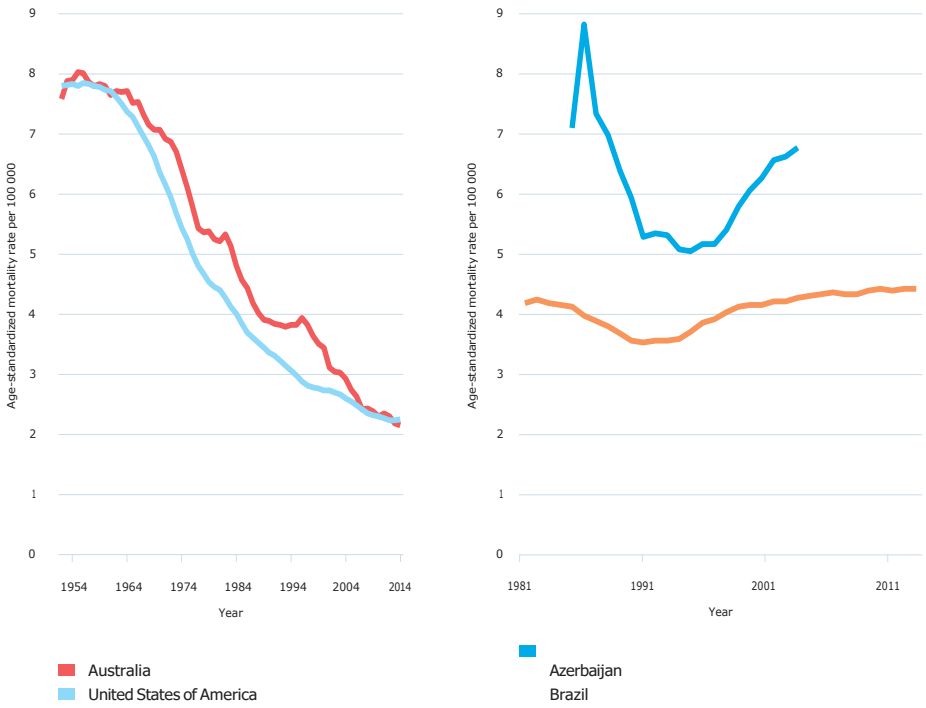

Figure I – Trends in childhood cancer mortality, comparing HIC with LMIC[7]

Geographic area, socioeconomic status of the family, gender, age and health care system play significant roles in contributing to disparities in the diagnosis and survival rates of childhood cancer. These disparities vary widely, with survival rates exceeding 80% in high-income countries (HIC), but dropping to around 50% in upper-middle-income countries (UMIC), and falling below 30% in both low-income countries (LIC) and low-middle-income countries (LMIC). On February 15, 2022, which marked International Childhood Cancer Day, the World Health Organisation (WHO) in the European Region launched the report *Childhood cancer inequalities in the WHO European Region* (WHO cancer inequalities). The report analyses the childhood cancer inequalities in the European Region across countries and even within the same country.

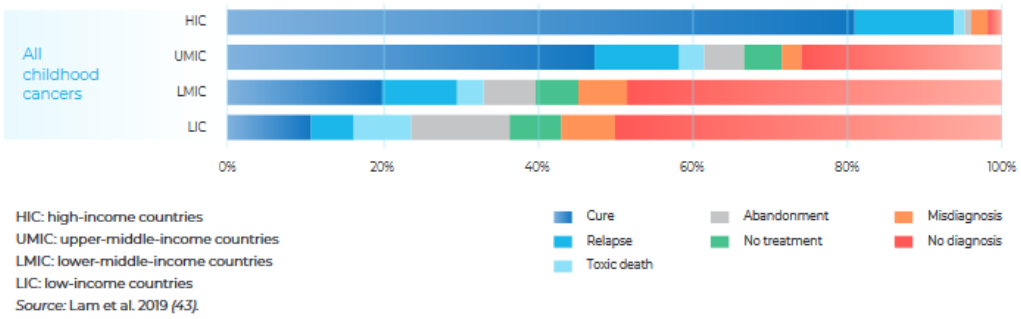

Figure II – Estimations of the factors contributing to lower survival in LIC[8]

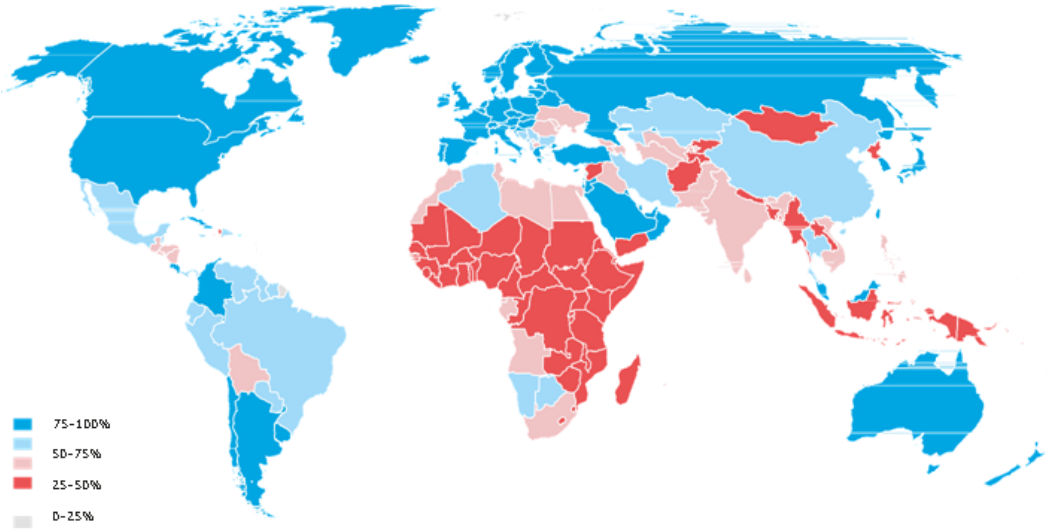

Figure III - Estimated childhood cancer 5-year net survival by country (2015–2019)[6]

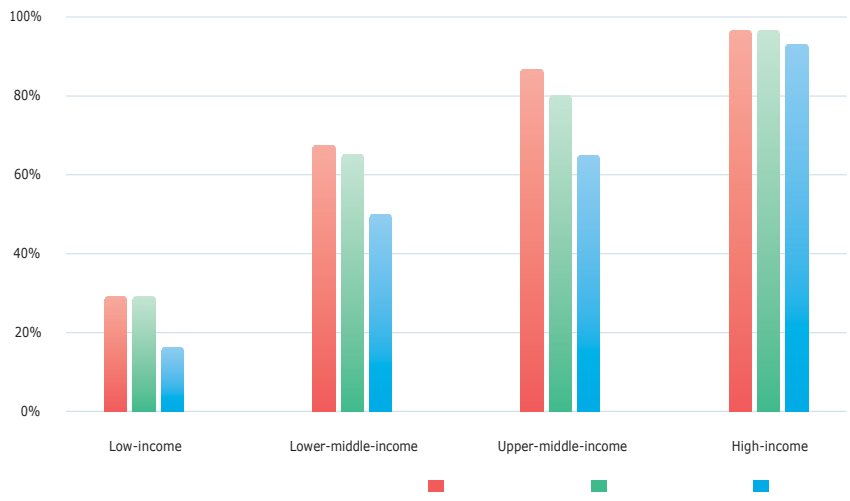

Figure IV - Percentage of countries with the availability of cancer services, by World Bank income group, 2019[6]

In Italy, data from AIRTUM (Associazione Italiana Registri Tumori) reported 7,000 new cancer cases among children and 4,000 among adolescents from 2016 to 2020. On an annual basis, there are on average 1,400 new cases among children aged 0 to 14 and 900 new cases among adolescents aged 15 to 19.

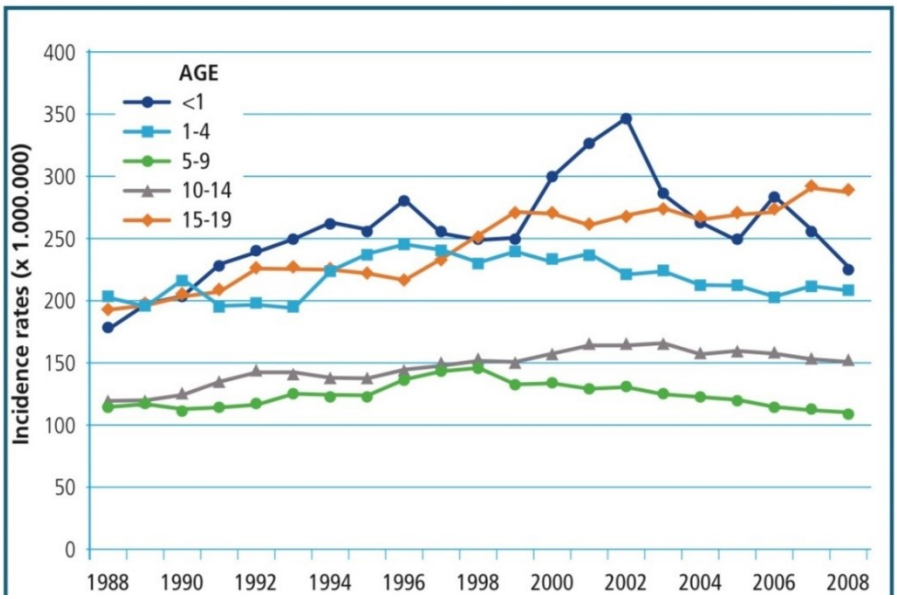

Figure V - Incidence rates of all malignant neoplasms in Italian children and adolescents by age group[10]

Childhood cancers are classified according to the International Classification of Childhood Cancer 3rd edition (ICCC-3)[9]. Among children leukaemia is the most frequent neoplasm accounting for 33% of all malignant cancers. This is followed by lymphomas at 16%, malignant tumors of the central nervous system (CNS) at 13%, neoplasms of the peripheral nervous system (PNS) at 8%, and tumors of the soft tissues at 7%. Other categories, including renal tumors, bone tumors, epithelial neoplasms, melanoma, neoplasms of the gonads, hepatic tumors, and retinoblastoma, each contribute approximately 1-5% to the overall total, collectively amounting to 23%. (Figure VI)[10].

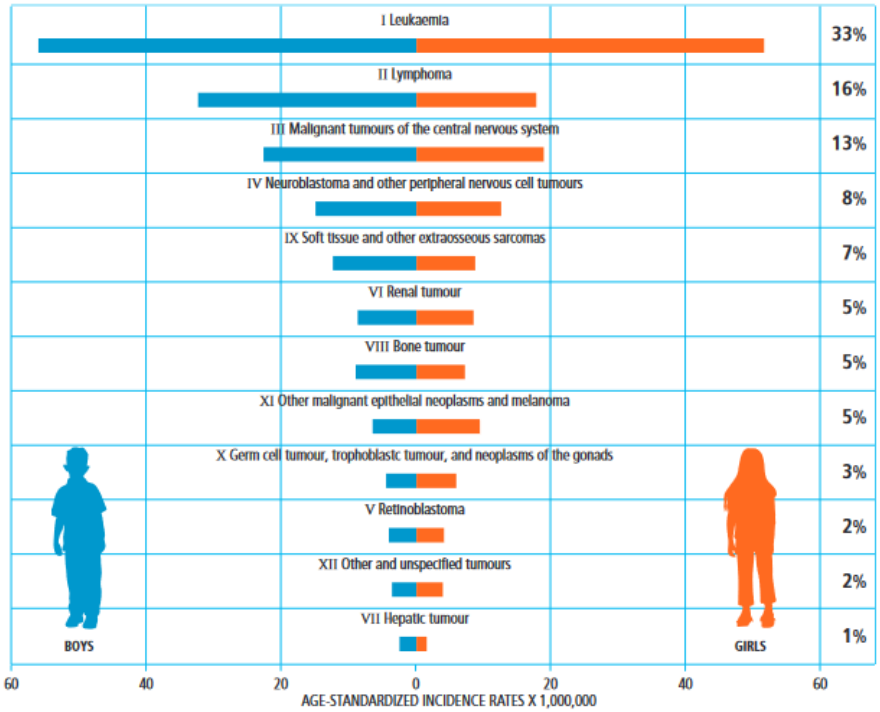

Figure VI - Age-standardized rates (European standard) by malignant cancer type (ICCC) and gender. 0-14 years age group. AIRTUM, 2003-2008[10].

Despite cancer representing a significant cause of mortality among children, outcomes have improved over the past few decades. In patients aged 0 to 14, malignant neoplasms have shown a remarkable increase in 5-year survival rates from 70% in 1988-1993 to 82% in 2003-2008[10] (Figure VII). Furthermore, when considering all childhood cancers collectively, 5-year survival rates across Europe have increased from 54% in 1978 –1982 to 75% in 1993 –1997[11], and approached 80% in 2005–2007[12]. These statistics reflect significant progress in the management and treatment of childhood cancers in Europe over the years.

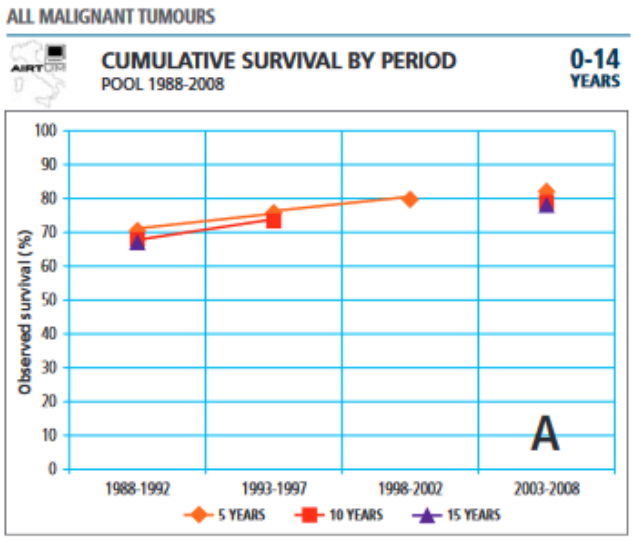

Figure VII - Time trends of 5-, 10-, and 15-year survival for all malignant neoplasms in children. AIRTUM, pool 1988-2008[10].

1.2 The HSCT

HSCT is a complex procedure in which hematopoietic stem cells (HSCs) are collected from a donor and then infused into a recipient. The aim of HSCT is to replace or repair damaged or diseased bone marrow and restore normal blood cell production and immune function. In 1957 *Thomas et al*. conducted the pioneering allogeneic HSCT. However, it was not until 1968 that the first successful allogeneic HSCT was achieved in patients with Severe Combined Immunodeficiency (SCID) by *Wiskott-Aldrich*.

Hematopoietic stem cells (HSCs) are a type of multipotent cells capable of differentiating into various mature blood cell types, including erythrocytes, lymphocytes, and thrombocytes. HSCs can be found within the bone marrow (BM), in peripheral blood (PB), particularly following chemo-mobilization, and in umbilical cord blood (UCB). The autologous HSCT requires the patient's own stem cells (auto-HSCT), whereas a donor's stem cells are used for an allogeneic HSCT (allo-HSCT). The selection of an appropriate allogeneic donor is based on histocompatibility between the donor and the recipient. In allo-HSCT, a matched sibling donor with compatibility at human leukocytes antigen (HLA)-A,-B and DR loci (6 out of 6 matches) is the preferred source of stem cells. In instances where no matched family donor is available, unrelated adult donors and unrelated cord blood

(CB) donors, ideally with a match of 7 or 8 out of 8 antigens at the HLA-A, -B, -C, and DRB1 loci, come into consideration. Alternatively, an haploidentical HSCT (haplo-HSCT) from related mismatched family donor may be considered. However, an HLA-identical related sibling or parental donor can be found for fewer than 25% of potential recipients[13].

The conditioning treatment is a crucial part of the HSCT procedure. This treatment regimen encompasses high-dose chemotherapy and, in certain cases, radiation therapy, such as total-body irradiation (TBI), along with monoclonal antibody therapy. Due to conditioning treatment patients may develop side effects, including aplasia, elevated susceptibility to infections, nausea, vomiting and fatigue. Furthermore, acute reactions resulting after infusion of HSCs are allergic reactions, fever, bradycardia, tachycardia, hypotension, respiratory distress, hemolytic reactions and sepsis.

The HSCT represents an important therapy option in the treatment of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), lymphoma and solid cancers. Moreover, the HSCT is a potentially curative treatment option for a spectrum of hematologic disorders, encompassing primary immunodeficiency, aplastic anemia, myelodysplasia, hemoglobinopathies and a range of genetic diseases[14].

1.3 HSCT complications

Patients undergoing HSCT are susceptible to both acute and chronic complications, some of which may require intensive treatment and admission to the intensive care unit (ICU). Among the most frequent acute complications are infections, hemorrhage, and graft-versus-host disease (GvHD).

In addition to acute complications, HSCT recipients may also confront late effects, which can manifest as secondary cancers, late-onset infections, impairments in quality of life, psychosocial challenges, as well as concerns related to sexual health and fertility[15]. These late effects can determine long-term challenges for children who have undergone HSCT.

1.3.1 Infective complications

Infections are one of the most common complications following HSCT, with reported incidence rates ranging from 13% to 60%[16]. Several factors related to HSCT contribute to an elevated risk of infectious complications, including neutropenia, cellular and humoral immune deficiencies and mucosal injury. Additionally, indirect transplant-related factors, such as the preparative regimen, graft source, donor type, and GvHD prophylaxis, can also influence the likelihood of infection [17].

The post-transplantation period can be divided into three phases: the initial 0-30 days, the following 30-100 days, and the period extending beyond 100 days. Each of these phases presents different mechanisms of immunodeficiency, and consequently, varying types of associated infections.

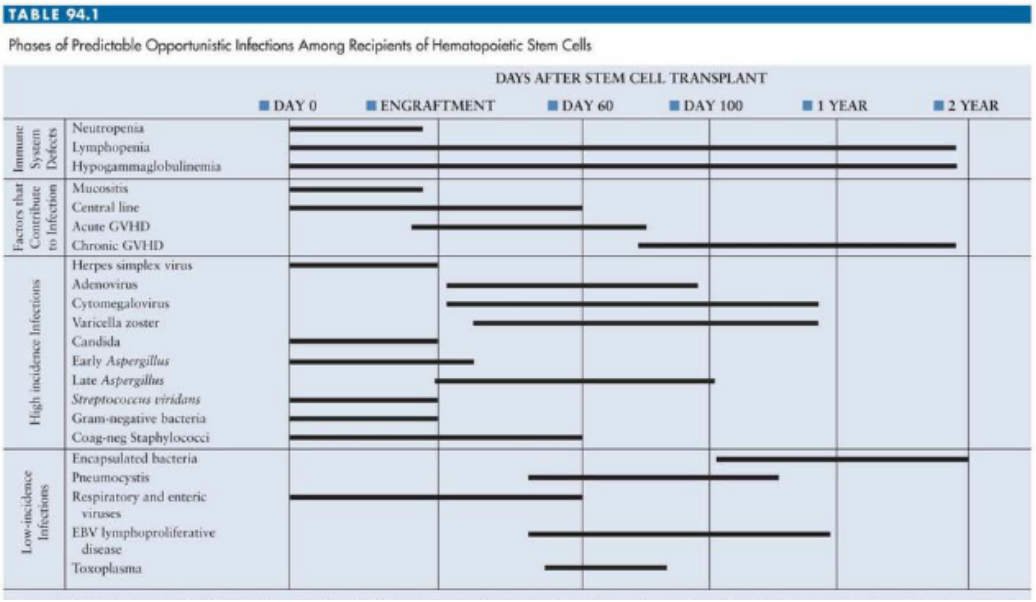

Figure VIII - Chronology of opportunistic infections after HSCT[13].

1.3.2 Pulmonary complications

Pulmonary complications are reported in a considerable part of transplant recipients, ranging from 30% to 60%, and they represent a major cause of mortality[18]. Among these complications, respiratory distress is frequently observed in transplant recipients and can result from various factors such as infections, hemorrhage, and pulmonary edema. It stands as a primary reason for admission to the ICU and contributes significantly to morbidity and mortality.

Pulmonary complications can be categorized into two main groups based on timing: acute complications occurring within the first 100 days post-transplantation and late complications emerging after this initial period. Moreover, they can be further classified into infectious and non-infectious complications (Table 1), each presenting its own set of challenges and management considerations.

Radiation, chemotherapy and the ongoing disease process can also lead to non-infectious pulmonary complications, characterised by interstitial disease, restrictive alteration and airway obstruction, all of which can potentially lead to respiratory failure. Pulmonary edema is a frequent complication during the early post-transplant period, especially in patients with fluid overload, renal or cardiac dysfunctions, or systemic inflammatory response syndrome (SIRS). Periengraftment respiratory distress syndrome (PERDS), characterised by fever, pulmonary edema and rash, typically resolves with the recovery of white blood cells. Patients with hypoxemia, dyspnea and diffuse infiltrates on chest X-ray may present diffuse alveolar hemorrhage, which can be treated with corticosteroids. The most common late complication during post-transplant phase, affecting approximately 10% of recipients, is bronchiolitis obliterans (BO). BO can be triggered by infection, chemotherapy toxicity and chronic GvHD (cGvHD). It manifests with progressively worsening dyspnea on exertion, non-productive cough and obstructive lung disease pattern, resulting from inflammatory and fibrous modifications of terminal bronchioles. A biopsy is required for the diagnosis and treatment typically involves bronchodilators and immunosuppressive therapy.

ACUTE COMPLICATIONS (0-100 days)	**LATE COMPLICATIONS (100+ days)**
Non-infectious complications • Pulmonary edema • Periengraftment respiratory distress syndrome (PERDS) • Diffuse alveolare haemorrhage (DAH) • Acute interstitial pneumonia • Transfusion related lung injury (TRALI) • Thrombotic microangiopathy (TMA)	**Non-infectious complications** • Bronchiolitis obliterans (BO) • Bronchiolitis obliterans organising pneumonia (BOOP) • Chronic GvHD
Infectious complications • Bacteria: Gram- rods and Gram+ cocci	**Infectious complications** • Bacteria: capsulated bacteria, Gram- rodes and Gram+ cocci • Virus: adenovirus, CMV, VZV, EBV

• Virus: HSV, CMV, Adenovirus, HHV6, RSV, Influenzavirus, Parainfluenzavirus, Rhinovirus, Metapneumovirus • Fungi: Candida spp., Aspergillus spp., Pneumocystis jirovecii	• Fungi: Candida spp., Aspergillus spp., Pneumocystis jirovecii

Table 1 - Pulmonary complications in HSCT patients[18]

TABLE 92.2

Pulmonary Complications after Hematopoietic Stem Cell Transplant

PHASE	INFECTIOUS	NONINFECTIOUS
Neutropenic phase (0–30 d)	Bacteria (20%–50%) Fungal (12%–45%)	Pulmonary edema Drug toxicity DAH
Early phase (30–100 d)	CMV pneumonitis (40%) PCP	Idiopathic pneumonia syndrome
Late phase (>100 d)	Uncommon except in GVHD	Bronchiolitis obliterans Cryptogenic organizing pneumonia Chronic GVHD

DAH, diffuse alveolar hemorrhage; CMV, cytomegalovirus; PCP, *Pneumocystis jiroveci (carinii)* pneumonia; GVHD, graft-versus-host disease.

Figure IX - Pulmonary complications in HSCT patients[13]

1.3.3 Graft failure

Graft failure (GF) is a rare yet highly dangerous complication that can occur after allo-HSCT. The incidence of GF in both patients who underwent auto-HSCT and allo-HSCT is generally less than 3-5%. However, in certain cases, such as haplo-HSCT or CB transplantation, the incidence can be as high as 10%.

The etiology of GF is multifactorial and involves various factors, including abnormalities in the donor's cells, anomalies in the recipient microenvironment, insufficiency in the conditioning regimen, medications, infections, immune-mediated graft rejection. Several risk factors have been identifies for graft failure, including HLA mismatch, a prolonged interval between diagnosis and transplantation (exceeding 6 months), the presence of splenomegaly, elevated serum ferritin level (greater than 1000 ng/mL), the use of a non-matched sibling donor and AB0 blood-type-mismatch.

Unfortunately, GF carries a poor prognosis, with most patients dying from infection or bleeding. The overall survival rate at 3–5 years after diagnosis is less than 20%. Early intervention, including supportive care, donor cell infusion and potentially a

second allo-HSCT, should be initiated as soon as possible to maximize the chances of a successful outcome.

1.3.4 GvHD

GvHD is one of the most common complications after HSCT, particularly in cases involving HLA mismatch.

In the 1960s, Billingham established criteria for the occurrence of GvHD:

- The administration of a graft containing immunocompetent cells, capable of mounting an immune response
- Immunological disparity between host and donor, typically involving the major histocompatibility complex (MHC) antigens or HLA
- The administration of the graft to an immunosuppressed host unable to reject the graft cells[19].

The original distinction between acute GvHD (aGvHD) and cGvHD was primarily based on the timing of onset following allo-HSCT. Traditionally, aGvHD was characterized by symptoms occurring before or around day 100 post-transplant, while cGvHD typically occurred after day 100. However, in recent years, this distinction has become more flexible for several reasons, including overlap in the clinical presentation, individual variability and evolution of transplantation practices[19].

The aGvHD represents the main cause of mortality within the first year following allo-HSCT. Approximately 40% of allo-HSCT recipients experience aGvHD, although the exact incidence is heavily influenced by factors such as the GvHD prophylaxis method employed and characteristics of the donor.

1.3.5 Other complications

Patients undergoing HSCT can also experience various complications affecting different organs. Heart complications are particularly prevalent in children who have undergone conditioning regimens involving cyclophosphamide and TBI. These patients may develop congestive heart failure, endocarditis, arrhythmias, and pericardial effusion. HSCT patients may present with abdominal pain, diarrhea,

gastrointestinal bleeding, enteritis, and, in severe cases, bowel perforation. Liver complications can also arise, often associated with sepsis and multi-organ failure (MOF). The most common liver complication is veno-occlusive disease (VOD), which may manifest around 30-40 days after HSCT, characterized by jaundice, fluid retention, weight gain, and hepatomegaly. Hepatitis can be induced by viral infections, autoimmune responses (autoimmune hepatitis or AIH), and drug-related liver injury.

Approximately 25-30% of children develop renal dysfunction in the initial three months following transplantation. Sepsis is a common trigger for acute kidney injury (AKI), with 25-40% of sepsis patients developing AKI during the early post-transplant phase. In these cases, AKI is associated with glomerular and tubular damage resulting from inflammatory cytokine cascades. Patients may also present with hepatorenal syndrome, characterized by a decreased glomerular filtration rate (GFR), sodium retention, hepatic dysfunction, peripheral edema, weight gain, and ascites. Hemorrhagic cystitis is another frequent complication, potentially leading to urinary bladder obstruction and postrenal failure. Renal failure management typically involves volume replacement, chemotherapy adjustments based on GFR, and, if necessary, renal replacement therapy (RRT). Additionally, hematologic and neurologic complications are common in HSCT patients. In severe cases, children may develop MOF, which stands as one of the leading causes for admission to the intensive care unit.

1.4 PICU admission

Children undergoing oncological treatment may present acute situations that need intensive care monitoring and support. 25-40% of oncologic patients are admitted to an intensive care unit at least once, due to underlying disease, therapy consequences and post-surgical monitoring, accounting for approximately 3% of all PICU admissions[20].

Even if children with onco-hematologic disease are just a minority of all intensive care unit accesses, their mortality rate is around 15-30% and can increase to 35% considering 90 days mortality. In comparison, children admitted after surgery have

a very low mortality rate (0-4%), their prognosis does not differ from that of the general population in the intensive care unit[21].

In their study, *Heying et al*. divided the patients into two groups: the first group included children admitted to the PICU due to complications caused by the underlying cancer before starting chemotherapy (respiratory insufficiency, tumor lysis syndrome), the second group included children admitted to the PICU because of complications of the oncological treatment, such as toxicity and infections. Patients in the first group received cytostatic therapy during the PICU stay and profited most from intensive care; the survival rate was 92%, comparable to the overall survival in the PICU. On the other hand, the survival rate of the second group of patients was 66% despite intensive care treatment. This data suggest that immunosuppression and chemotherapy can lead to complications that require intensive care treatment.

1.4.1 PICU in transplanted children

HSCT children represent a high-risk group of fragile patients, since they are often immunologically depressed because of underlying disease or immunosuppressive therapy. HSCT is considered to be an independent risk factor for both PICU admission and mortality, because it increases the risk for infections, hemodynamic instability and pulmonary failure[1]. Studies report different percentages of HSCT patients admitted to PICU: from 10-20%[22],[23] to 35-40%[24],[25],[26].

The risk factors associated with PICU admission are underlying haematological disease, allogeneic HSCT, undergoing more than one HSCT, use of total body irradiation (TBI)[22] and GvHD.

Patients admitted to the PICU due to major acute complication after HSCT have a severe prognosis and worse outcome compared to non-HSCT patients. Increased mortality is associated with MOF, need for invasive mechanical ventilation, cardiac dysfunction[27], neutropenia or GvHD, previous myeloablative chemotherapy, and pre-transplant malnutrition[26].

The mortality rate for transplanted children admitted to the PICU has improved during the past years: children transplanted before 2000 had a mortality rate ranging

from 45%[28],[29] to 70%[30],[31],[32], reaching 90% in case of need for mechanical ventilation [33],[34]. More recent studies on children transplanted after 2000 show a lower mortality rate of 20-60%[24],[25],[32],[35],[36],[37], even for patients requiring mechanical ventilation (42-61%[38],[25],[39]). Results may show high variability because most of them are single-centre studies; more recently the subject was analysed by multicentric studies[38],[39],[35],[40].

Survival rates are increasing due to innovations and research in the field of transplantation and to the development of the intensive care treatment[36],[41],[27]. The main factors related to prognose improvement are the introduction of non-myeloablative regimens, better antimicrobial prophylaxis, improved antifungal therapy, lung protective ventilation strategies and early use of non-invasive ventilation[42].

1.4.2 PICU in non-transplanted children

The onco-hematologic disease itself and the consequences of chemotherapy and radiotherapy may result in severe complications and life-threatening conditions, which can require intensive care. Even though just a small percentage of non-HSCT patients require intensive care (2-4%), the mortality rate is still high (25-35%[43],[1]). However, if compared to HSCT patients, non-HSCT children have not only a lower PICU admission rate but also a lower mortality.

Major causes of PICU admission are respiratory failure, neurologic failure, sepsis, organ failure and seizures[1]. Negative prognostic factors include disseminated intravascular coagulation (DIC), hemodynamic instability, renal failure, cardiac arrest and multiorgan failure.

1.5 Causes of PICU admission

Even though a nationwide consensus has not been achieved yet, the most diffuse criteria for pediatric intensive care unit admission are the following: respiratory failure with 30% increase in basal respiratory rate (RR) or $SatO_2$ <92% on room air, severe sepsis, neurologic compromise, renal failure with fluid overload, oliguria, electrolyte derangements and continuous renal replacement therapy

(CRRT), liver failure with severe hypocoagulability, liver support, hepatic encephalopathy.

The majority of PICU admissions are due to respiratory failure, pARDS (pediatric Acute Respiratory Distress Syndrome) and sepsis. Other causes are neurological problems, renal dysfunction, tumor lysis syndrome.

1.5.1 Sepsis

In 2005 the International Pediatric Sepsis Consensus Conference (IPSCC) defined sepsis as SIRS in presence of or as a result of suspected or proven infection. SIRS was defined as the presence of at least two of the following criteria (one of which must be abnormal temperature or impaired leukocyte count): core temperature >38,5° or <36°, tachycardia or bradycardia for children younger than 1 year old, tachypnea or need for mechanical ventilation, age-related elevated or depressed leukocyte count[44].

Age Group[a]	Heart Rate, Beats/Min[b,c]		Respiratory Rate, Breaths/Min[d]	Leukocyte Count, Leukocytes × 10^3/mm^3[b,c]	Systolic Blood Pressure, mm Hg[b,c,e,f]
	Tachycardia	Bradycardia			
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 yr	>180	<90	>34	>17.5 or <5	<100
2–5 yrs	>140	NA	>22	>15.5 or <6	<94
6–12 yrs	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 yrs	>110	NA	>14	>11 or <4.5	<117

Figure X – Age-specific vital signs and laboratory variables[44].

In 2016 the Third International Consensus Definition for Sepsis (Sepsis-3) updated the definition of sepsis in adult patients as life-threatening organ dysfunction caused by a dysregulated host response to infection[45]. Since the applicability of these criteria to pediatrics was limited, the Society of Critical Care Medicine (SCCM) launched in 2019 the Pediatric Sepsis Definition Taskforce, in order to validate criteria for the definition of sepsis in children[46]. The results of the Pediatric Sepsis Definition Taskforce's international survey was published by *Morin et al*. in June 2022[47]. Accordingly to the research, the most shared definition of sepsis was life-threatening organ dysfunction that is remote from the primary site of infection.

Moreover the IPSCC definition was perceived to be the most useful for sepsis recognition, while the Sepsis-3 definition was classified as slightly more useful for benchmarking, disease classification, research, and prognostication[47].

The definition of septic shock was based on clinical signs of poor perfusion (cold, pale, mottled skin, increased capillary refill time, altered neurologic function, low urinary output, increased lactate), organ dysfunction indicated by laboratory results, need for hemodynamic support through fluid bolus or vasoactive-inotropic therapy and sepsis scores.

Children undergoing cancer treatment or HSCT are at risk of long duration neutropenia and impaired mucosal barrier, that can lead to the development of febrile neutropenia and eventually sepsis. Frequent sites of infection are the respiratory tract, the gastrointestinal tract, central lines, skin and soft tissues. Sepsis in neutropenic patients can arise from neutropenic enterocolitis, with fever, abdominal pain and diarrhea, although this classic triad is not always present. The treatment consists of bowel rest and intravenous antibiotics; in case of perforation, bleeding, peritonitis or obstruction surgery may be required. Sepsis can also be a complication of a community-acquired pneumonia, caused by pathogens such as influenza virus, parainfluenza virus, respiratory syncytial virus and cytomegalovirus, candida and aspergillus. If fever persists more than 3-5 days after beginning of antibiotics, antifungal treatment should also be administered[59].

CLINICAL RISK FACTORS	LABORATORY-BASED RISK FACTORS
Evidence of shock	Elevated C-reactive protein > 10 mg/L
Near-myeloablative chemotherapy (leukemia induction or delayed intensification)	Absolute neutrophil count < 200 cells/mm^3
Allogeneic hematopoietic stem cell transplant recipient	Absolute monocyte count < 100 cells/mm^3
Relapsed leukemia	Platelet count < 50,000/mm^3
Poorly controlled solid malignancies	Gram-negative bacteremia
Pneumonia	
Neutropenic enterocolitis	
Invasive fungal infection	
Severe oropharyngeal mucositis	
Prolonged neutropenia (>7 d)	
High presenting temperature (>39°C)	
High-dose cytosine arabinoside	
Age less than 1 y	

Figure XI – Clinical and laboratory high risk factors in febrile neutropenia[13]

Higher mortality has been reported for septic patients with severe acute malnutrition, chronic conditions, oncologic disorders, hypotension, use of

inotropes, mechanical ventilation, decreased level of consciousness and low GCS. Impaired laboratory parameters such as VIS, base deficit, pH, lactate, platelets, fibrinogen, urea, creatinine, albumin, potassium, ALT, and procalcitonin may also have a negative prognostic relevance[48].

1.5.2 Respiratory failure

Respiratory failure is defined as the inability to maintain either the normal delivery of oxygen to tissues or the normal removal of carbon dioxide from the tissues. From a physiologic perspective, respiratory failure can be caused by diffuse pulmonary dysfunction (ventilation/perfusion [V/Q] mismatch or pulmonary shunt), neurologic dysfunction (depression of the respiratory drive), cardiac dysfunction (low cardiac output or pulmonary edema), or a lack of hemoglobin to transport gases[49]. Hypoxic acute respiratory failure (ARF) is defined by PaO_2<60 mm Hg; hypercapnic respiratory failure is defined by $paCO_2$>50 mm Hg.

Hypoxic acute respiratory failure is characterized by severe hypoxemia (PaO2/FiO2 ratio <300), leading to respiratory acidosis and evident clinical signs of respiratory distress. Typical symptoms are severe dyspnea with accessory muscle use, tachycardia, hypertension and mental status changes. The most common pulmonary causes of hypoxemia are hypoventilation, low inspired fraction of oxygen, presence of an intrapulmonary shunt, ventilation-perfusion inequality and diffusion limitation. The most common etiology for hypoxemia in critically ill children is an altered V/Q ratio due to impaired lung ventilation and perfusion. Atelectasis (ie, pneumonia or mucous plug) and pulmonary edema (ie, SIRS, ARDS, cardiac failure) lead to worsening V/Q mismatching and, therefore, to hypoxia. An effective approach to oxygenation should address both the symptomatic treatment of hypoxemia and the support of the increased workload on the respiratory muscles. Hence, treatment aims to improve oxygenation and unload inspiratory muscles while preserving the lungs from injuries[50].

Hypercapnia can be caused by reduced tidal volume due to opioid or benzodiazepine overdose, that cause respiratory depression, neuromuscular diseases and post traumatic flail chest; another major cause of hypercapnia is increased dead space due to hyperinflation (obstructive airway diseases or

excessive PEEP), low cardiac output, pulmonary hypertension and pulmonary embolism. Hyperinflation compromises respiratory muscles function increasing the end expiratory lung volume. This leads to decreased muscle fibre length and force as well as to mechanical disadvantage in the diaphragm.

Decreased tidal volume	**Increased dead space**

Sedative overdose:
• Opioid
• Benzodiazepine
	Hyperinflation:
	• Obstructive airway disease
	  • Asthma
	  • Bronchiolitis
	  • Cystic fibrosis
	• Excessive PEEP on mechanical ventilator

Neuromuscular weakness • Central nervous system disease • Spinal cord injury/inflammation • Peripheral nerve disorder • Neuromuscular junction disease • Myopathy • Metabolic derangements	Decreased cardiac output • Dehydration • Dysrhythmia • Myocarditis/cardiomyopathy • Post cardiopulmonary bypass
Flail chest (post trauma)	Increased pulmonary vascular resistance
	Pulmonary embolism

Table 2 - causes of hypercapnia[51]

Acute respiratory failure is a common complication in critically ill patients admitted to PICU, as it affects approximately two thirds of PICU patients. Causes of acute respiratory failure include upper airway obstruction, lower airway obstruction, restrictive lung disease, central nervous system disorder, peripheral nervous system and muscle disorders.

Location	**Example**
Upper airway obstruction	• Infection (croup, epiglottitis, bacterial tracheitis) • Laryngotracheomalacia • Foreign body • Anaphylaxis
Lower airway obstruction	• Asthma • Bronchiolitis • Cystic fibrosis
Restrictive lung disease	• Acute respiratory distress syndrome • Pleural effusion • Pneumonia • Pulmonary edema • Abdominal compartment syndrome
Central nervous system disorder	• Intracranial injury (hemorrhage, ischemia) • Medication (sedatives) • Metabolic encephalopathy

Peripheral nervous system and muscle disorders	• Guillian Barre´ syndrome • Muscular dystrophy • Scoliosis • Spinal cord injury • Botulism • Intoxications

Table 3 - Etiologies of acute respiratory disease in children[51]

The acute respiratory distress syndrome (ARDS) was defined by the Berlin Definition in 2012 [52]. In 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed the pediatric definition of ARDS, updated to PALICC-2 in 2023 (Figure XII)

Age (DS 1.1)	Exclude patients with perinatal lung disease		
Timing (DS 1.2)	Within 7 d of known clinical insult		
Origin of edema (DS 1.3)	Not fully explained by cardiac failure or fluid overload		
Chest imaging (DS 1.3)	New opacities (unilateral or bilateral) consistent with acute pulmonary parenchymal disease and which are not due primarily to atelectasis or pleural effusion[a]		
Oxygenation[b] (DS 1.4.1)	IMV: OI ≥ 4 or OSI ≥ 5 NIV[c]: $Pao_2/Fio_2 \leq 300$ or $Spo_2/Fio_2 \leq 250$ **Stratification of PARDS severity:** Apply ≥ 4 hr after initial diagnosis of PARDS (DS 1.4.4)		
	IMV-PARDS: (DS 1.4.1)	Mild/moderate: OI < 16 or OSI < 12 (DS 1.4.5)	Severe: OI ≥ 16 or OSI ≥ 12 (DS 1.4.5)
	NIV-PARDS[c] (DS 1.4.2; DS 1.4.3)	Mild/moderate NIV-PARDS: $Pao_2/Fio_2 > 100$ or $Spo_2/Fio_2 > 150$	Severe NIV-PARDS: $Pao_2/Fio_2 \leq 100$ or $Spo_2/Fio_2 \leq 150$
	Special populations[d]		
Cyanotic heart disease (DS 1.6.1; DS 1.6.2)	Above criteria, with acute deterioration in oxygenation not explained by cardiac disease		
Chronic lung disease (DS 1.6.3; DS 1.6.4)	Above criteria, with acute deterioration in oxygenation from baseline		

Figure XII – The PALICC-2 definition of pARDS [53]

1.5.3 Multiorgan failure (MOF)

Multiorgan failure (MOF) is a severe life-threatening condition in which two or more organ systems fail to function adequately. Critically ill children may develop MOF due to disease, infection, sepsis, major trauma, burns or surgery. The pathophysiology of MODS is complex and often begins with a primary insult or injury that triggers an inflammation response in the body. The widespread immune response leads to release of inflammatory mediators such as cytokines and chemokines and to activation of immune and endothelial cells. Blood vessels' permeability increases leading to microvascular dysfunction, impaired blood flow to vital organs, tissue hypoxia, mitochondrial dysfunction with cell damage and

organ dysfunction. The impaired pro-inflammatory mechanism further contributes to tissue damage and organ dysfunction. Different organs may be involved as the insult and the inflammatory response persist. The sequence of events and the extent of organ involvement can vary based on the underlying cause, patient characteristics and other factors. Early recognition and intervention are critical in the management of MODS: addressing the underlying insult and providing supportive care can prevent further organ dysfunction and improve patients' outcomes.

1.5.4 Neurologic compromise

Children with oncologic conditions may face neurologic compromise due to underlying disease and treatments and may require PICU admission. Seizures and neurotoxicity can be caused by chemotherapy, radiotherapy and underlying brain metastases. In case of brain tumor or brain metastases children can develop headaches, altered mental status and eventually herniation due to increased intracranial pressure, requiring constant monitoring and adequate management in PICU. Cancer and its treatments may also increase the risk of thrombotic events or vascular complications, leading to strokes and cerebrovascular compromise, as well as to encephalopathy and delirium, which may manifest as confusion, altered mental status and behavioural changes. Oncologic therapy may also cause metabolic imbalances and electrolytes abnormalities that affect the nervous system. Some oncologic conditions can result in neuromuscular complications and need of respiratory support. Neurologic complications may also be caused by intrathecal chemotherapy and HSCT, due to conditioning regimens and GvHD. Neurologic compromise may vary depending on type of cancer, stage of disease, treatments received and individual factors. Treatment aims to address neurological symptoms and underlying oncologic condition and to prevent potential complications.

1.5.5 Renal failure

Renal failure is a common cause of PICU admission in children with cancer and is associated with higher risk of complications, longer PICU stay and mortality, as well as increased use of renal replacement therapy and mechanical ventilation[54].

The KDIGO guidelines describe the epidemiology of acute kidney injury and stage AKI according to plasma creatinine level and urine output in 3 stages (Figure XIII).

KDIGO	1	SCr rise ≥0.3 mg/dL within 48 hr or an increase in creatinine of ≥50% within 7 day	>0.5 and ≤ 1 mL/kg/hr
	2	Increase in creatinine of ≥100%	>0.3 and ≤ 0.5 mL/kg/hr
	3	Increase in creatinine of ≥200% or SCr ≥4 mg/dL or receipt of dialysis or eGFR<35 mL/min/1.73 m^2	≤ 0.3 mL/kg/hr
		(neonatal cut-off, SCr >2.5 mg/dL)	

Figure XIII - KDIGO staging of acute kidney disease

The RIFLE classification has been modified for children (Figure XIV)

	Estimated CCl	Urine output
Risk	eCCl decrease by 25%	<0.5 ml/kg/h for 8 h
Injury	eCCl decrease by 50%	<0.5 ml/kg/h for 16 h
Failure	eCCl decrease by 75% or eCCl <35 ml/min/1.73 m^2	<0.3 ml/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure >4 weeks	
End stage	End-stage renal disease (persistent failure >3 months)	

eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease.

Figure XIV - Pediatric-modified RIFLE (pRIFLE) criteria[55]

AKI in oncologic children can be caused by chemotherapy-induced nephrotoxicity due to chemotherapy drugs such as cisplatin, methotrexate and ifosfamide. Children manifest decreased urine output, fluid retention and edema, elevated serum creatinine (SCr) and electrolytes imbalances. Other symptoms such as nausea and vomiting, abdominal pain, fatigue, fever, change in mental status, hematuria, proteinuria and pale skin may be present. In particular, in the critically ill population the consequences of fluid overload are associated to higher risk of morbidity and mortality and can lead to longer hospital and PICU stay and prolonged need of ventilator support[56],[57]. However, the clinical presentation of AKI can vary widely depending on the cause and severity of the condition. Additionally, some symptoms may be more subtle in infants and young children, making early recognition and diagnosis challenging.

In some cases cancer can directly infiltrate the kidneys, causing tissue damage and impaired renal function; tumor or metastatic lesions can cause obstruction of the urinary tract, resulting in hydronephrosis and AKI. HSCT patients may often

develop renal failure due to complications of HSCT, such as GvHD, conditioning regimens, nephrotoxic drugs and radiation nephropathy. Other causes of AKI in oncologic patients are sepsis, dehydration and electrolytes imbalances, tumor-related hypercalcemia, hypertension and glomerular disease triggered by cancer treatments.

1.5.6 Tumor lysis syndrome

Tumor lysis syndrome is a life-threatening emergency in children with cancer. It occurs frequently in malignancies with large tumor burden, highly chemotherapy sensitive tumors, such as Burkitt lymphoma, lymphoblastic lymphoma, leukemia, and occasionally in solid tumors. The destruction of tumor cells following the beginning of cytotoxic therapy and the subsequent release of nucleic acids, which are than broken down into uric acid, phosphate and potassium, in the bloodstream can result in metabolic and electrolyte alterations, mainly hyperphosphatemia, hyperuricemia, hyperkalemia and hypocalcemia. Clinical presentation has its onset 12-72 hours after cytotoxic treatment initiation and is characterised by fatigue, lethargy, anorexia, nausea and vomiting, fluid overload, congestive heart failure, dysrhythmia, seizures, muscle cramps, tetany and eventually sudden death. Uric acid and calcium phosphate can precipitate in renal tubule, causing obstructive uropathy and acute kidney injury, with flank pain, haematuria, hypertension, edema, oliguria snd eventually anuria; hyperkalemia can cause nausea and vomiting, muscle cramps, paresthesia and cardiac arrhythmias. Moreover, hyperphosphatemia results in secondary hypocalcemia, that can cause seizures, dysrhythmia and tetany.

Diagnosis of tumor lysis syndrome is based on the following laboratory tests: uric acid ≥ 8mg or 25% uric acid increase from baseline, potassium ≥ 6mg/dL or 25% potassium increase from baseline, phosphorus ≥ 6,5 mg/dL or 25% phosphorus increase from baseline, calcium ≤ 7mg/dL or 25% calcium decrease from baseline. Clinical diagnosis is defined as one of the following in addition to laboratory TLS: increase in serum creatinine by ≥ 1.5 times the upper limit of normal (ULN), cardiac arrhythmia or sudden death, or seizure[58].

1.6 High-level treatments

1.6.1 HFNC (High-Flow Nasal Cannula)

High-flow nasal cannula (HFNC) oxygen therapy is a method that involves administering a high flow of heated and humidified gas via nasal prongs. Originally employed as a primary treatment for respiratory distress syndrome and apnea of prematurity in pre-term neonates, has now extended its use to pediatric and adult intensive care. It is a simpler and easier technique compared to non-invasive ventilation (NIV) and appears to be a promising alternative treatment for hypoxemic acute respiratory failure (ARF). Unlike NIV, where the gas flow rate is adjusted to maintain a predetermined constant inspiratory pressure support (PS) and positive end-expiratory pressure (PEEP), in the HFNC system the continuous flow rate of gas leads to variable pressures in the airways according to the patient's breathing effort and dynamic thoracic compliance. The continuous delivery of high flow creates resistance during exhalation, producing positive pressure, which is however significantly diminished when the patient opens his mouth. HFNC provides a high fraction of inspired oxygen (FiO2) and generates a low level of positive end-expiratory pressure (PEEP). Moreover, it facilitates the washout of dead space in the upper airways, leading to improved mechanical properties of the lungs and reduced strain on inspiratory muscles. However, due to air leakage, pressure levels tend to be variable and the use of large nasal prongs might result in nasal obstruction.

The HFNC appears to be better tolerated compared to non-invasive ventilation (NIV) and standard oxygen therapy. The heated humidifier used in HFNC ensures that the gas provided to the patient has a similar level of humidity as that found in the alveoli, with an absolute humidity of approximately 44mg/L of water. This leads to better comfort with less dyspnea feeling, as well as to improved compliance[50].

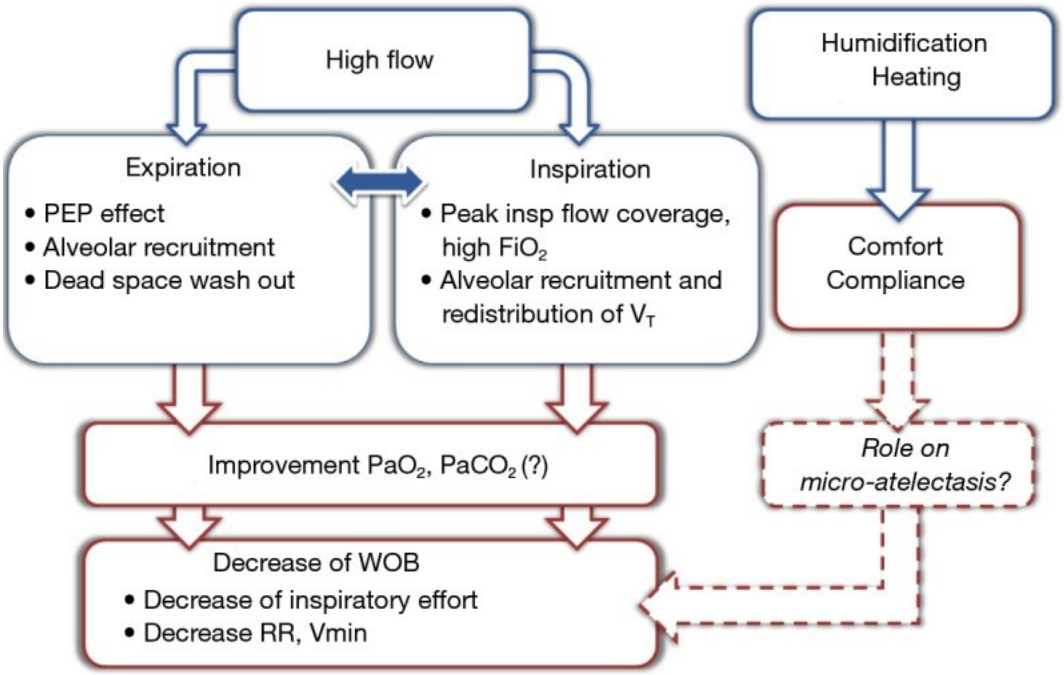

Figure XV - Physiological effects of HFNC oxygen therapy[50]

Studies on immunocompromised patients report that HFNC may improve the outcomes of patients admitted to PICU: intubation rate[59],[60] and mortality rate[61],[62] in patients treated with HFNC alone are lower compared to those treated by NIV with HFNC between NIV sessions.

1.6.2 NIV (Non-Invasive Ventilation)

NIV (non-invasive ventilation) delivers mechanical respiratory support through a face mask connected to a humidification system, without the use of an endotracheal airway. It most frequently involves a combination of pressure support (PS) ventilation and positive end-expiratory pressure (PEEP), or simply the application of continuous positive airway pressure (CPAP). The combination of PS and PEEP improves oxygenation and unloads respiratory muscles, however, it may potentially compromise lung protection. NIV tolerance can sometimes be difficult due to frequent mask leaks that may lead to asynchrony between the patient and the ventilator, eventually requiring intubation.

NIV is used for ARDS treatment when hypoxia and respiratory distress persist or worsen despite administration of oxygen therapy via nasal cannula or face mask, preventing patients from the potential complications related to invasive mechanical ventilation. These complications include laryngeal or tracheal injury, airway

edema, vocal cord dysfunction, ventilator-associated pneumonia, requirement for substantial sedation and the associated complications. Additionally, the use of NIV can help shorten ICU/hospital stays and promote better outcomes. A multicentre study from *Morris et al* shows that children receiving NIV present less mortality, shorter length of ventilation, shorter length of stay and increased number of ventilator-free days compared to children receiving invasive ventilation as first-line treatment after PICU admission[63]. Signs of success of NIV should be seen within the first hours after initiation of treatment and include improvement of oxygen saturation and eventually resolution of hypoxia, decreased respiratory and heart rates related to decreased respiratory strain, clinical signs of lung recruitment and improvement of clinical conditions. NIV success should be assessed within the first hours of initiation to avoid delayed procedures of intubation and invasive mechanical ventilation. Patients with high aspiration risk, altered mental status, cardiac arrest, pneumothorax, upper airway injury and airway edema are contraindicated for therapy with NIV. Independent risk factors of NIV failure are shown to be sepsis, shock, vasoactive use, multi-organ dysfunction, moderate to severe PARDS, oncologic diagnosis and elevated respiratory rate at 4 hours of NIV. Complications of NIV are facial skin lesions, eye irritation, gastric insufflation, barotrauma due to the generation of high tidal volumes under positive pressure, subcutaneous emphysema, pneumothorax, air leak syndrome, aspiration and hemodynamic instability[64].

1.6.3 IV (Invasive Ventilation)

More than 20% of PICU patients require endotracheal intubation and invasive mechanical ventilation to support their respiratory function. The most common indication for invasive ventilation (IV) is respiratory failure due to compromised lung function, reduced lung compliance, airway obstruction, pARDS, severe asthma, bronchiolitis; non-respiratory indications include neurological impairment, neuromuscular diseases, congenital heart diseases and cardiac conditions, hemodynamic shock and post-surgical care.

The endotracheal tube (ETT) used for endotracheal invasive ventilation is placed into the patient's trachea and connected to the ventilator, which is set on specific ventilation modes and parameters according to the patient's needs and condition.

Common ventilation modes are Assist-Control (AC) mode, Synchronised Intermittent mandatory Ventilation (SIMV) mode, Pressure Support Ventilation (PSV) mode, Continuous Positive Airway Pressure (CPAP) mode, Pressure-Controlled Ventilation (PCV) mode; common ventilation parameters are Tidal Volume (Vt), Respiratory Rate (RR), Inspiratory-to-Expiratory Ratio (I:E Ratio), Positive End-Expiratory Pressure (PEEP), Fraction of Inspired Oxygen (FiO_2), Peak Inspiratory Pressure (PIP), Pressure Support Level (PS). Controlled ventilation provides breaths regardless of the patient's respiratory effort; assisted ventilation supports the patient in every breath providing volume and pressure and eventually gives breaths at a set rate in case of failed breath initiation. Continuous monitoring and adjustment are essential to provide optimal invasive ventilation in pediatric patients. The patient's conditions are monitored by vital parameters, including heart rate, respiratory rate, blood pressure, oxygen saturation (SpO2), arterial blood gases (ABGs), chest X-rays and capnography. Despite the development of several studies, there is limited evidence on weaning strategies and criteria for extubation in PICU remain unclear. Extubation failure is reported in 2-20% of cases and is not associated with duration of invasive mechanical ventilation. The child's readiness for weaning from mechanical ventilation should be continuously assessed by monitoring for signs of spontaneous breathing and stable oxygenation; ventilation support should be eventually gradually decreased.

Barotrauma (delivery of too high inflating pressure), volutrauma (delivery of too large tidal volumes) and electrauma (repetitive opening and closing surgical of alveoli) have been recognised as the underlying mechanisms inducing pulmonary inflammation and causing lung damage. Lung protective strategies with lower tidal volume (<10ml/kg), lower peak inspiratory pressure (<30cmH_2O) and higher PEEP (positive end-expiratory pressure) have been developed in the past few decades to reduce ventilation-induced lung injuries (VILI). Despite this, invasive mechanical ventilation frequently causes complications, such as atelectasis, post-extubation stridor, perioral tissue damage, ventilator associated pneumonia, mucus plugging, pneumothorax, pneumomediastinum, and ICU neuromyopathy. Hence, specialists need to early identify and treat complications. Complications may vary based on age, underlying condition, mode and duration of ventilation.

The most frequent complication of IV in pediatric patients is atelectasis, defined as partial collapse or incomplete inflation of the lung. The use of positive pressure to increase airway pressure to a higher level than the critical opening pressure may result in hyperinflation of lung segments; PEEP is often successfully used as treatment. Perioral tissue damage and pressure ulcer may be caused by prolonged use of endotracheal tube. Prevention strategies include frequent monitoring of mechanical pressure on the oral mucosa and repositioning of the endotracheal tube. Ventilator associated pneumonia is defined as pneumonia occurring in patients after more than 48 hours of mechanical ventilation and is mostly caused by micro-aspirations. Lung injury may also be due to excessive airway pressure (barotrauma) or excessive tidal volumes causing overdistention of alveoli (volutrauma) leading to pneumothorax, pneumomediastinum and subcutaneous emphysema. Children with long PICU stay may also develop neuromyopathy leading to weakness and atrophy of the diaphragm and increased oxygen demands of the respiratory muscles (that can reach 20-50% of total body oxygen delivery), exposing them to higher risk of extubation failure. Neuromyopathy also contributes to mucus plugging, since cough reflex and pooling of secretions may be involved. The use of sedatives worsens the situation by impairing muco-ciliary clearance and cough mechanism. Treatment of mucus plugging consists in mucolytic agents, chest physiotherapy, intermittent percussive ventilation and cough assist. Post-extubation stridor occurs in 5% of patients undergoing IV for more than 48 hours and is frequently associated with reintubation procedure. Other complications of mechanical ventilation are acquired subglottic stenosis, oxygen toxicity, hypotension and hemodynamic instability. Children requiring comfort medications to ensure safe activity levels of mechanical ventilation may develop delirium, tolerance and withdrawal, that may impact on clinical outcomes. Additionally, prolonged mechanical ventilation may lead to psychological distress, anxiety and post-traumatic stress.

1.6.4 High-Frequency Oscillatory Ventilation (HFOV)

High-Frequency Oscillatory Ventilation (HFOV) is a form of nonconventional ventilation used in neonatal intensive care unit (NICU) and in PICU. Unlike other high-frequency ventilation forms it provides an active expiratory phase. Indications for the use of HFOV are restrictive lung disease, cardiac disease, acute respiratory failure and chronically ventilated children[65],[66]. However, HFOV has not been

proven to be effective in reducing mortality in cases of acute hypoxic respiratory failure neither in adults nor in children.

1.6.5 Renal replacement therapy (RRT)

AKI often occurs in critically ill patients and is associated to higher risk of mortality, that can reach 30-50% in children requiring renal replacement therapy (RRT)[67]. Moreover, pediatric AKI is associated with prolonged critical care admissions, increased mechanical ventilation needs, and longer overall hospitalizations[68].

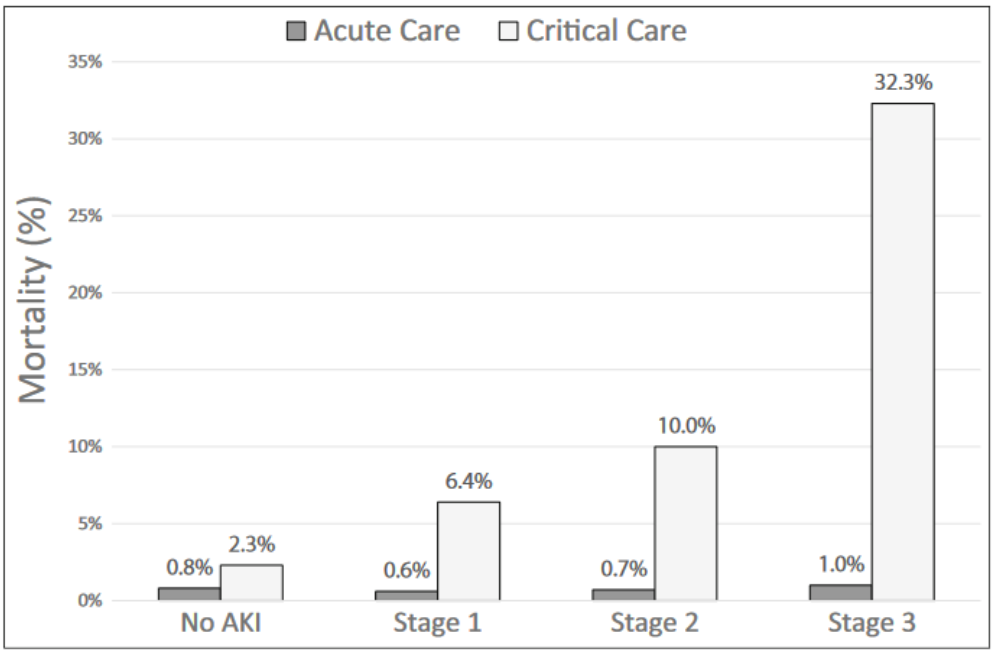

Figure XVI – Children mortality in hospitalized children by AKI severity stage (67)

In case of severe AKI, renal replacement therapy (RRT) is often required. Both Continuous Renal Replacement Therapy (CRRT) and Intermittent RRT effectively manage metabolic conditions and to date no superiority has been established between these modalities in terms of mortality outcomes. In the past few years there has been a in the AKI epidemiology: while AKI was previously primarily associated with single-organ failure arising from intrinsic renal issues or toxin exposure, it now often develops within the context of multiple organ dysfunction. The severity and complexity of this condition contribute to the high mortality rate associated with AKI in the PICU, which can reach approximately 50% for children requiring RRT. Moreover, the role of renal replacement therapies has evolved from addressing immediate life-threatening situations such as acid-base imbalances or

electrolyte irregularities to managing the complications of complex diseases, such as oliguria, fluid overload, impaired oxygenation and ventilation.

Indications for the initiation of a renal replacement therapy (RRT) include volume overload, severe metabolic acidosis, electrolyte abnormalities (hyperkalemia, hyponatremia, hyperphosphatemia), uremia with eventually encephalopathy and pericarditis, intoxication and progressive or persistent AKI.

Volume overload in case of AKI occurs as a result of the kidney's inability to regulate fluid balance effectively and may manifest even in patients without oliguria or anuria. RRT should be considered when fluid overload does not respond to diuretics and compromises organ function. Children who have undergone HSCT are at high risk of fluid overload due to voluntary intravenous hyperhydration, infusion of multiple antibiotics, veno-occlusive disease, and multiple transfusions of blood products. In addition, the conditioning regimen may be associated with renal toxicity and with some degree of systemic inflammatory response syndrome accompanied by a capillary leak syndrome(21). Metabolic acidosis is caused by renal failure due to impaired acid renal excretion. In this case, RRT may be initiated when pH<7.1 or serum bicarbonate level<12mmol/L. Hyperkalemia is the most life-threatening electrolyte abnormality associated with AKI: potassium levels>6.5 mmol/L despite medical treatment are an indication for initiation of renal replacement therapy, as well as hypernatremia, hyponatremia and hyperphosphatemia.

However, there are neither specific indications nor defined levels of serum creatinine, cystatin C and blood urea nitrogen that define the optimal timing for initiation of RRT in pediatric patients. Early initiation of RRT is associated with improved survival, due to early optimization of volume status, correction of acid-base and electrolyte imbalances and management of azotemia. However, risks associated with RRT, including complications of the vascular access, such as vascular injury, thrombosis, hemorrhage and infection, and intradialytic hypotension should also be carefully considered. Furthermore, RRT might interfere with the subsequent recovery of kidney function. Hence, clinicians must consider individual patient factors before deciding on the appropriate timing for initiating

RRT. The ultimate goal is to balance the potential benefits of early intervention while minimizing the potential risks and adverse outcomes associated with RRT.

The choice of the RRT method for PICU patients is typically influenced by several factors, such as the resources available within the institution, the expertise of the medical team, specific patient characteristics and treatment goals. Patient size should especially be taken into consideration, since small patients can present significant technical difficulties in establishing dialysis access due to their size.

The IHD (Intermittent Hemodialysis) is a form of RRT involving a dialyser, most commonly consisting of numerous hollow fibres arranged in a parallel structure, resembling the human capillary network. Dialyzer's characteristics and surface area determine clearance rate of small solutes. Effective dialysis aims to limit the amount of blood within the dialyzer while ensuring sufficient clearance of solutes.

CRRT (Continuous Renal Replacement Therapy) operates similarly to IHD but at considerably lower flow rates and continuously. Compared to peritoneal dialysis, CRRT provides more efficient clearance and easier regulation of fluid removal. CRRT is recommended by the KDIGO Clinical Practice Guideline for AKI in hemodynamically unstable patients, since it enables a prolonged clearance of metabolites and toxins while ensuring a gradual and predictable fluid removal process. Catheter placement, usually in the right internal jugular vein, may be technically challenging to obtain for neonates and small children.

Complications during continuous renal replacement therapy (CRRT) are common and include catheter-related complications, extracorporeal circuit-related complications, hypotension, hypothermia, electrolyte disturbance and incorrect medication dosing.

In patients with coagulopathy, thrombocytopenia or active hemorrhage, anticoagulation during CRRT is often avoided. In case anticoagulation is needed, either heparin (unfractioned heparin or low-molecular-weight heparin) or citrate may be used. The use of heparin as an anticoagulant can lead to complications such as bleeding and heparin-induced thrombocytopenia, a condition characterized by reduced platelet levels due to heparin exposure. On the other hand, citrate anticoagulation, alternatively used to heparin, may cause citrate toxicity due to

citrate accumulation. If calcium is insufficiently replaced during citrate anticoagulation, hypocalcemia may occur. Additionally, both metabolic acidosis and metabolic alkalosis can be observed in patients undergoing citrate anticoagulation. The choice of anticoagulant and its management should be adapted to the patient's specific medical needs and condition to minimize the risk of adverse outcomes. Electrolyte impairments should also be monitored during RRT. Hypotension can occur in one third of patients and is mostly related to ultrafiltration, which can exacerbate hemodynamic instability in patients undergoing CRRT. In case hypotension is associated with volume depletion, it can be managed by volume reinfusion and adjustment of ultrafiltration targets. CRRT, unlike IHD, usually does not make use of warm dialysate and replacement fluids; this can result in moderate thermal losses with hypothermia and vasoconstriction, that may improve hemodynamic stability on one hand, but on the other hand may mask the onset of fever.

A safe and effective RRT for pediatric patients is peritoneal dialysis. Extracorporeal circuit and anticoagulation are not needed. Peritoneal dialysis tends to cause less hemodynamic instability in comparison to hemodialysis due to its more physiologic and less proinflammatory process.

1.6.6 Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal Membrane Oxygenation (ECMO) is an advanced life-support therapy for patients with respiratory, cardiac or combined cardiopulmonary failure refractory to conventional management. An outflow cannula is used to drain blood from the patient to a membrane lung, where gas exchanges (oxygenation and decarboxylation) and blood rewarming take place. Blood is than reinfused into the patient’s circulation. The membrane lung consists of thin, semi-permeable tubes resembling the alveoli that facilitate diffusion across their surfaces. Depending from the patient’s conditions, ECMO can be administered as veno-arterial (VA) ECMO or veno-venous (VV) ECMO.

Indications for ECMO Support	Contraindications to ECMO
Oxygenation index > 40	EGA < 30 weeks
PaO2/FiO2 ratio < 60	Weight < 1.5 kg
pH < 7.25	Lethal chromosomal abnormality
Shock	Anticipated poor neurologic outcome or irreversible brain injury
A-aDo2 > 500 mmHg	Severe intracranial hemorrhage (≥Grade III);
PIP or Pplat > 30 cmH_2O	Uncontrolled bleeding Mechanical ventilation for >14 days

Figure XVII – ECMO support indications and contraindications

VA ECMO is used in patients with heart disease, cardiac failure, cardiac shock, periprocedural support for cardiac interventions or as a bridge to longer term VAD (Ventricular Assist Device) support or transplant. Typical cardiac indications include refractory low cardiac output (cardiac index <2 L⁄min⁄m2) and hypotension (systolic blood pressure <90 mmHg) despite adequate intravascular volume, high dose inotropic agents and intra-aortic balloon pump(69). Blood is drained from a drainage cannula, usually placed percutaneously in the internal jugular vein or in the right atrium, oxygenated and warmed through the circuit of the membrane lung, than reinfused via an arterial line to a major systemic artery, mainly the internal carotid artery, bypassing both the lungs and the heart. The ECMO circuit is connected in parallel to lung and heart.

Veno-venous ECMO is employed to provide temporary respiratory support to patients with severe lungs dysfunction, allowing the lungs to recover. In comparison with VA ECMO, the oxygenated blood is reinfused through the infusion catheter into the patient's venous system and the circuit is connected in series to the heart and lungs. Indications for VV ECMO treatment are ARDS, pneumonia, bridge to lung tansplantation, pulmonary hemorrhage or massive haemoptysis, diaphragmatic hernia and meconium aspiration in neonates.

VA ECMO	VV ECMO
• Provides cardiac support to assist systemic circulation	• Does not provide cardiac support to assist systemic circulation
• Requires arterial and venous cannulation	• Requires only venous cannulation
• Bypasses pulmonary circulation/decreases pulmonary artery pressures	• Maintains pulmonary blood flow
• Could be used in RV failure	• Can't be used
• Lower perfusion rates are needed	• Higher perfusion rates are needed
• Higher PaO_2 is achieved	• Lower PaO_2 is achieved
• ECMO circuit connected in parallel to the heart and lungs	• ECMO circuit connected in series to the heart and lungs

Table 4 - Differences between Veno-arterial (VA) and Veno-venous (VV) Extracorporeal Membrane Oxygenation[69]

Contraindications to VA ECMO and VV ECMO include severe neurologic compromise, uncontrollable hemorrhage, incurable malignancy, prematurity (< 30 weeks gestation), low birth weight (< 1 kg).

Complications may often present during ECMO treatment and can be associated to the ECMO procedure itself or to the underlying disease of the patient. ECMO for pulmonary support has a lower rate of complications and a higher rate of survival compared to ECMO for cardiac support. Patients receiving ECMO after ECPR (extracorporeal cardiopulmonary resuscitation) report the worst outcomes. 10-30% of patients undergoing ECMO develop hemorrhage: bleeding risk increases due to heparinisation, platelet dysfunction and clotting factor hemodilution and can occur at cannula site, at surgical site, intrathoracic, abdominal, retroperitoneal. Pulmonal and intracranial hemorrhage are also frequent. The occurrence of systemic thromboembolism due to extracorporeal circuit clotting is a relatively rare complication, though associated with severe consequences. Neurological compromise manifests with seizures, infarction and intracranial hemorrhage and is associated with a lower survival rate. Moreover, other medical complications associated with ECMO treatment are hypertension with eventually hemorrhage and stroke, hypoxia, electrolyte imbalance leading eventually to arrhythmias, oliguria, acute tubular necrosis, hypo or hyperglycaemia and sepsis.

1.6.7 Total Parenteral Nutrition (TPN)

In 2005 the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR) published the Guidelines on Paediatric Parenteral Nutrition. The Guidelines were developed and updated in 2018 together with the Chinese Society of Parenteral and Enteral Nutrition (CSPEN)[70].

Food intake should provide sufficient nutrients to maintain the body's tissues and permit growth, especially during infancy and adolescence, when basal and anabolic requirements are particularly high. Insufficient nutrition during crucial growth phases leads to higher risk of growth failure and nutritional disorders. Over the past few decades, techniques for artificial nutritional support have been developed, enabling children that cannot be orally or enterally fed to be treated with parenteral nutrition, so that they don't suffer from malnutrition-related complications. Parenteral nutrition can be both used for short-term and long-term parenteral feeding.

Parenteral nutrition (PN) supplies children with nutritional energy required for basal metabolic rate (BMR), physical activity (PA), diet induced thermogenesis (DIT), growth and eventually correction of pre-existing malnutrition. Nutritional status, underlying diseases, energy intake, energy losses, age and gender may affect energy needs. Estimation of total required calories should take into consideration weight gain in regard to the target growth and required catch-up growth, recommended intake of the different macronutrients, tolerance to PN administration, such as hyperglycaemia, hypertriglyceridemia, liver enzyme abnormalities, cholestasis, tolerance of cyclic administration. Daily energy can be calculated on the basis of different equations, that usually add to the calculated basal metabolic rate of healthy children the increased expenditure due to stress, disease, injury, activity and growth[71]. Components of the parenteral nutrition are amino acids, lipids, carbohydrates, vitamins, iron, minerals and trace elements (chromium, copper, iodine, manganese, selenium and zinc), fluid and electrolytes (Na, Cl and K).

Complications may present in children undergoing TPN. CVC (central venous catheter) related infection should be suspected in case of fever, metabolic acidosis, thrombocytopenia and glucose instability. Moreover, TPN may present metabolic or nutritional complications due to deficiency or excess of PN components (electrolytes, minerals, glucose, essential fatty acids, vitamins). Other TPN related complications include hepatobiliary disease, metabolic bone disease and growth impairment.

1.7 Prognostic Scores

1.7.1 PEWS (Pediatric Early Warning Score) and O-PEWS

Oncologic patients are a high risk population due to underlying disease, therapy toxicity and immunosuppression. They can require unplanned PICU admission and present higher mortality rate. Early detection of complications may lead to early treatment and therefore ultimately improve outcomes. However, the medical team needs to identify the right time for PICU admission: a late referral can compromise the prognosis due to worsening conditions, on the other hand an early admission exposes the patient to the risks of intensive care treatment. Additionally, intensive care resources should be administered as rationally as possible. Hence, objective operator-unrelated indicators for PICU admission are needed in order to predict the potential progression of the patient's clinical conditions and ensure treatment consistency. Therefore, various early warning scores have been developed to early detect patient's clinical deterioration, that is often preceded by changes in vital parameters such as heart rate, blood pressure, respiratory rate, level of consciousness. A reliable score should be non-invasive, objective, reproducible and quick to assest.

The first developed PEWS was the Brighton PEWS in 2005, which considered patient's behaviour, cardiovascular system and respiratory system[72]; in 2009 the BedsidePEWS developed by *Parshuram et al.,* ranging from 0 to 26 points, included systemic blood pressure, capillary refill time, heart rate, respiratory rate, respiratory effort, oxygen saturation and oxygen therapy as parameters, excluding behaviour. It showed a high sensitivity for detecting patients at high risk of cardiac arrest[73]. The validity of the PEWS has been tested in various studies, such as a

retrospective study by *Akre*[77] (2010), that showed a PEWS sensitivity of 85% to predict deterioration as early as 11 hours before the acute event. Similar results emerged in another study where sensitivity for PICU admission was 84.2% at a score≥4[74]. Moreover, it was demonstrated that the PEWS was able to early identify 87% of children at risk of clinical deterioration in the 24 hours before the event[75].

The study by *Agulnik et al*. analyses the use of a PEWS in an onco-hematological population. The Children's Hospital Early Warning Score takes into consideration behaviour, cardiovascular system, respiratory system, staff concern and family concern. The study shows that the score is strongly related to unplanned PICU admission in oncohematological patients and in HSCT patients. Compared to the control group, a significant increase in the score is already present 11 hours before PICU admission, which aligns with other studies indicating that the beginning of vital parameter fluctuations may begin 12-24 hours before an acute event.

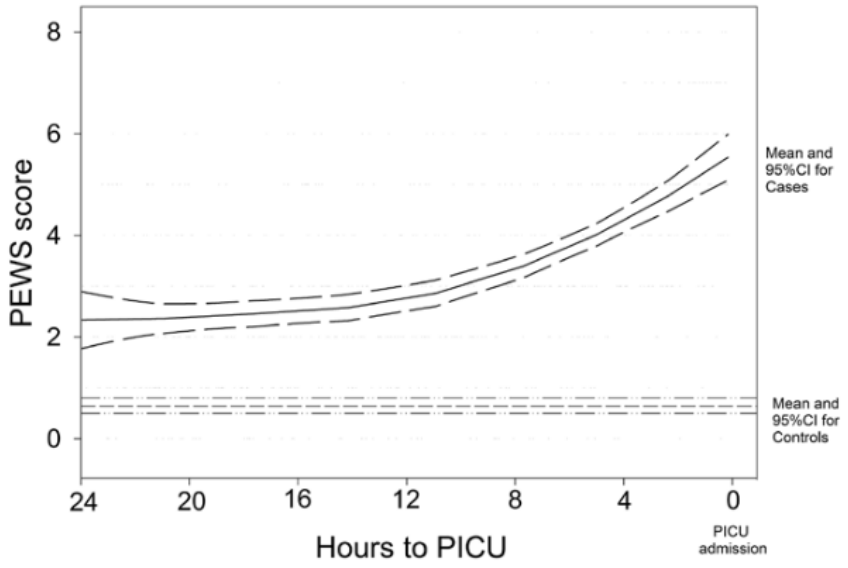

Figure XIII - PEWS trend over time preceding unplanned PICU admission[76]

Furthermore, the study also confirms the relationship between high PEWS values before PICU admission and higher mortality rate in the PICU, as well as longer hospital stay.

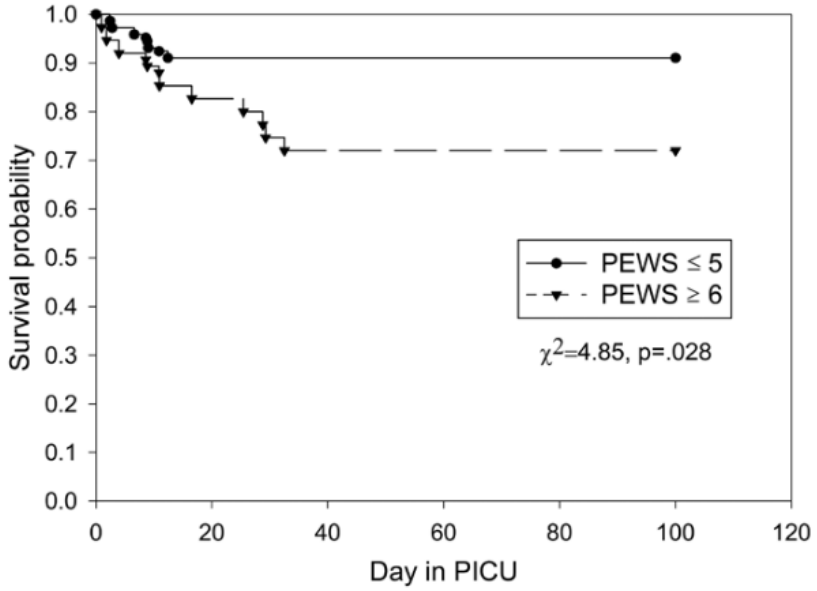

Figure XIX - Kaplan-Meier curve of PICU deaths among unplanned PICU transfers related to PEWS score[76]

The prospective cohort study by *Soeteman et al.* validates a modified BedsidePEWS in pediatric oncologic patients to predict clinical deterioration. The score is significantly associated to deterioration of clinical condition, unplanned PICU admission and CPR (cardio-pulmonar resuscitation).

The PEWS used in our study is the Oncological Pediatric Early Warning Score (O-PEWS) developed by Italian Pediatric Onco-Hematology Association (AIEOP). It modifies Monaghan's Brighton PEWS to specifically evaluate oncologic patients' conditions, though remaining an objective, non-invasive and quick to asses score. The O-PEWS examines the cardiovascular, respiratory, neurocognitive and urinary systems and assigns a score ranging from 0 to 3 points for each parameter, for a maximum score of 15. Additionally, an extra point can be assigned in case of caregiver and/or operator concern. The O-PEWS hasn't been validated yet and no literature has been published.

O-PEWS score	0	1	2	3	Max score
Level of consciousness/behaviour	Appropriate for the age	Irritable	Somnolent but awakenable	Lethargic, confused	3
Heart rate	Normal for the age*	Upper limits for the age*	Tachycardia[a]	Tachycardia[b] or bradycardia	3
Systolic blood pressure	Normal for the age*	Upper limits for the age*	Hypotension or Hypertension[c]	Hypotension or Hypertension[d]	3
Respiratory function	Sat 0_2 98-100 % in AA	Sat 0_2 94-95 % in AA or need of 2-4 L/min 0_2 or tachypnea[e]	Sat 0_2 92-95 % in AA with Vmk 30-40% or high flow 0_2 [f] or tachypnea[g] or nasal flaring	Sat 0_2 >90 % in AA with Vmk 50 % or high flow 0_2[h] or need of NIV or dyspnea/need of accessory muscles	3
Diuresis	≥ 2 mg/kg/h	< 2 mg/kg/h	Need of diuretics	Any response to diuretics	3
Total					15

AA: ambient air; Vmk: Venturi mask; NIV: non-invasive ventilation; [a] Increase of 20% of the basal heart rate; [b] Increase of 30% of the basal heart rate; [c] Increase or decrease of 20% of the basal value; [d] Increase of 50% or decrease of 30% of the basal value; [e] Increase of 20% of the basal respiratory rate; [f] High flow with Fi0_2 30-40% or 0_2 6-8 L; [g] Increase of 30% of the basal respiratory rate; [h] High flow with Fi0_2 50% or 0_2 > 8 L.

Table 5 – O-PEWS Score

1.7.2 PELOD Score (Pediatric Logistic Organ Dysfunction)

The PELOD (Pediatric Logistic Organ Dysfunction) score was first developed in 1999 and validated in 2003 by *Leuteurtre et al.*; in 2013 the score was updated (PELOD-2)(77). It now includes 10 variables involving five organ systems (cardiovascular, respiratory, renal, hematologic, neurologic and hepatic systems) and describes the severity of multiple organ dysfunction in critically ill patients. It objectively evaluates different organs' status and predicts the patient's prognosis. The organ dysfunction variables are: GCS and pupillary reaction (neurologic system); lactatemia, MAP (cardiovascular system); creatinine (renal system); PaO_2, $PaCO_2$, need of invasive ventilation (respiratory system); white blood cells (WBC)

count and platelets count (hematologic system). The individual scores for each organ are than summed up to calculate the overall PELOD score. A higher PELOD-2 score is related to increased severity of multiple organ dysfunction; as a prognostic indicator, it is associated to the patient's prognosis and mortality risk. In their study *Leteurtre et al.* showed that PELOD-2 has good discrimination (AUC of 0.94) and good calibration (Hosmer and Lemeshow goodness-of-fit test). The score correlates with number of organ dysfunctions and therefore with mortality rate (Figure XX).

Organ dysfunctions and variables	**Points by severity level**						
	0	**1**	**2**	**3**	**4**	**5**	**6**
Neurologic							
• Glasgow coma score	≥11	5-10			3-4		
• Pupillary reaction	Both reactive					Both fixed	
Cardiovascular							
• Lactatemia (mmol/L)	<5.0	5.0-10.9			≥11.0		
• Mean arterial pressure (mmHg) (months)							
0-<1	≥ 46		31-45	17-30			≤ 16
1-11	≥ 55		39-54	25-28			≤ 24
12-23	≥ 60		44-59	31-43			≤ 30
24-59	≥ 62		46-61	32-44			≤ 31
60-143	≥ 65		49-64	36-48			≤ 35
≥144	≥ 67		52-66	38-51			≤ 37
Renal							
• Creatinine (µmol/L) (months)							
0-<1	≥ 69		≥ 70				
1-11	≥ 22		≥ 23				
12-23	≥ 34		≥ 35				
24-59	≥ 50		≥ 51				
60-143	≥ 58		≥ 59				
≥144	≥ 92		≥ 93				
Respiratory							
• PaO_2 (mmHg)/FiO_2	≥ 61		≤ 60				
• $PacO_2$ (mmHg)	≥ 58	59-94		≥ 95			
• Invasive ventilation	No			Yes			
Hematologic							
• WBC Count ($x10^9$/L)	>2		≤ 2				
• Platelet ($x10^9$/L)	≥142	77-141	≤ 76				

Relationship between number of organ dysfunctions, PELOD-2 score, and mortality rate		
Number of organ dysfunctions	PELOD-2 Score Mean (SD)	Mortality rate (%)
0	0 (0.0)	0.4
1	2.3 (0.8)	0.3
2	4.9 (1.3)	1.2
3	7.5 (2.0)	7.1
4	11.5 (4.4)	30.5
5	16.8 (5.2)	59.0

SD = Standard deviation

Figure XX – PELOD Score

1.7.3 PIM Score (Pediatric Index of Mortality)

The PIM score was first developed by *Shann* in 1997 to evaluate pediatric patients' conditions and to early recognise those at higher risk of poor outcome[78]. It has been updated to PIM 2 in 2003[79] and to PIM 3 in 2013[80]. The PIM 3 score is calculated from 10 clinical and physiological variables collected in the first hour after PICU admission (Figure XXI). A higher PIM score indicates a greater severity of illness and is associated with an increased risk of mortality.

Variable
Pupils fixed to light? (Yes/No)
Elective admission (Yes/No)
Mechanical ventilation in the first hour (Yes/No)
Absolute value of base excess (mmol/L)
SBP at admission (mm Hg)
$SBP^2/1{,}000$
$100 \times Fio_2/Pao_2$ (mm Hg)
Recovery post procedure?
Yes, recovery from a bypass cardiac procedure
Yes, recovery from a non-bypass cardiac procedure
Yes, recovery from a noncardiac procedure
Very high-risk diagnosis (Yes/No)
High-risk diagnosis (Yes/No)
Low-risk diagnosis (Yes/No)
Constant

SBP = systolic blood pressure.

Figure XXI - PIM 3 variables[80]

1.7.4 POPC Score (Pediatric Overall Performance Category)

Over the past few decades, overall mortality in the intensive care has decreased, thus ensuring higher-quality lives post-treatment has also become a primary goal of PICU. Therefore, assessing morbidity is an important part of pediatric outcomes research, especially in studies with a high risk of decreased functional status due to neurologic involvement. The Pediatric Overall Performance Category (POPC)

scale was developed to describe cognitive impairment and is used to evaluate performance in children. It ranges from 0 (normal function) to 6 (death) points (Figure XXII).

Score	Category	Description
1	Good overall performance	PCPC = 1; healthy, alert, and capable of normal activities of daily life
2	Mild overall disability	PCPC = 2; possibility of minor physical problem that is still compatible with normal life; conscious and able to function independently
3	Moderate overall disability	PCPC = 3; possibility of moderate disability from noncerebral systems dysfunction alone or with cerebral system dysfunction; conscious and performs independent activities of daily life but is disabled for competitive performance in school
4	Severe overall disability	PCPC = 4; possibility of severe disability from noncerebral systems dysfunction alone or with cerebral system dysfunction; conscious but dependent on others for activities of daily living support
5	Coma or vegetative state	PCPC = 5
6	Brain death	PCPC = 6

Figure XXII - Pediatric Overall Performance Category (POPC)[81]

2. AIM OF THE STUDY

The first objective of the study is the description of a population of onco-hematologic pediatric patients who had been admitted to Italian Pediatric Intensive Care Units (PICUs) between January 2019 and April 2022. The second objective of the study is to identify risk factors associated to PICU mortality and length of PICU stay.

3. MATERIALS AND METHODS

3.1 Study setting

We conducted an observational multicentric study composed by a retrospective and a prospective phase involving 14 Italian Pediatric Intensive Care Units (Bergamo, Bologna, Brescia, Firenze, Genova, Messina, Milano Buzzi-Sacco, Padova, Roma ARCO, Roma DEA, Torino, Trieste, Verona and Vicenza).

The promoter of the study was Terapia Intensiva Pediatrica Azienda Ospedale Università di Padova.

The study has been conducted in collaboration with Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana and Associazione Italiana di Ematologia e Oncoematologia Pediatrica (AIEOP).

The study design adhered to the Declaration of Helsinki principles for medical research involving human subjects. Consent was given by the patient's parents before enrollment. The Ethics Committee for Clinical Trials of the Provincia di Padova (University Hospital of Padova), expressed its favorable approval in regard to the Clinical Trial in question titled “Respective and prospective analysis on risk factors and outcome in cancer patients admitted in Italian Pediatric Intensive Care Units: a multicenter study” at the meeting held on June 17, 2021 with Protocol n. CESC 5068/AO/21. The protocol was registered on the Clinical Trials Registry (ID NCT NCT04581655).

3.2 Study population

Data were collected from a total of 538 patients affected by onco-hematological disease that were admitted to PICU between January 2019 and April 2022. 239 patients were enrolled in the retrospective study and 299 in the prospective study. 110 out of 538 patients were admitted to PICU after surgery and stayed in the intensive care unit for less than 48 hours. These patients were considered only for the first objective of the study.

The inclusion criteria were:
- oncologic diagnosis in patients between 0 and 18 years of age;

- pediatric intensive care unit admission
- agreement to the informed consent.

Exclusion criteria were:

- lack of consent to data collection

3.3 Data collection

Data about the clinical course of onco-hematological patients admitted to the PICU during the study period of time were gathered through ONCOTIPNET, a database created by a network of Italian pediatric intensive care units. Data were collected in an Excel file reporting: 1) patients' characteristics and variables related to the before-PICU admission phase; 2) variables during PICU stay.

More in details we considered:

1) Variables before PICU admission: age, sex, ethnicity; Hospital, date of admission to hospital; underlying disease, treatment phase; type of transplant, development of HSCT-related complications; provenience (emergency room, ward of the same hospital, ward of another hospital, PICU of another hospital); PICU admission cause: post-surgical surveillance, cardiovascular insufficiency, neurological insufficiency, respiratory insufficiency (upper airways, lower airways, others), renal insufficiency, gastrointestinal/hepatic insufficiency, others; treatments received before PICU admission: HFNC, NIV, hemofiltration, hemodialysis, vasoactive amines, others; presence of multiorgan failure or pARDS; O-PEWS; PIM 3 score; POPC score.

   For the O-PEWS we collected the following data: consciousness level and behaviour, heart frequency, respiratory frequency, MAP, SpO_2, FiO_2, need of NIV, diuresis, need of diuretics.

   For the PIM 3 score we collected the following data: age, pupillary reaction, need for mechanical ventilation in the first hour, absolute value of base excess (BE), systolic blood pressure (SBP) at admission, FiO_2/PaO_2, lactatemia, if the patient was admitted electively, if the patient was admitted post procedure (recovery form a bypass cardiac procedure, recovery from a

non-bypass cardiac procedure, recovery from a noncardiac procedure), diagnosis risk (very high risk, high risk, low risk).

The POPC score is assessed by the intensivist based on the patient's ability and disability level.

2) Variables during PICU stay: priority levels for PICU admission; date of admission to the PICU, date of discharge from PICU, length of PICU stay; PELOD score; presence or development of organ failure (respiratory failure, heart failure, renal failure), multiorgan failure, pARDS; medical procedures and required treatments: pericardial drainage catheter, thoracic drainage catheter, abdominal drainage catheter, tracheostomy, surgical procedure, dialysis, total parenteral nutrition (TPN), Extracorporeal Membrane Oxygenation (ECMO), PIC monitoring, central venous catheter (CVC), midline, arterial line; ventilation support (invasive and non-invasive ventilation); drugs for analgesia and sedation; development of abstinence syndrome, delirium; cardiac arrest; presence of infection, antibiotic, antiviral, antifungal therapy; sepsis (Glasgow Coma Score (GCS), serum creatinine, bilirubin, platelets, PaO_2, FiO_2, SaO_2, PaO_2/FiO_2, SaO_2/FiO_2, MAP); POPC score at PICU discharge; mortality outcome in PICU, after 30 days from PICU discharge, after 90 days from PICU discharge.

   For the PELOD score we collected the following data: date of score's assessment, age; neurologic variables: GCS, verbal, motoric and pupillary reaction; respiratory variables: PaO_2, FiO_2, PaO_2/FiO_2, $PaCO_2$ (Partial Pressure of Carbon Dioxide), need for mechanical ventilation; cardiovascular variables: lactatemia, MAP; renal variables: serum creatinine; hematologic variables: WBC (White Blood Cell) count, platelet count. The PELOD score was calculated at first, second and discharge day.

   Regarding the presence of respiratory failure, we collected the following variables: PaO_2 (Partial Pressure of Oxygen), SpO_2 (Saturation of Peripheral Oxygen), MAP (Mean Arterial Pressure), FiO_2 (Fraction of Inspired Oxygen), PaO_2/FiO_2 (Ratio of the Partial Pressure of Oxygen to the Fraction of Inspired Oxygen), SpO_2/FiO_2 (Ratio of the Saturation of Peripheral Oxygen to the Fraction of Inspired Oxygen), OI (Oxygenation Index), OSI

(Oxygen Saturation Index); presence of Pediatric Acute Respiratory Distress Syndrome (PARDS).

3.4 Definitions

Tumor diagnosis was divided into hematological tumor (LLA, LMA, MDS, HL, NHL) and solid tumors.

Treatment phase was divided into 3 groups:

- phase 1: on therapy;
- phase 2: off therapy;
- phase 3: therapy not yet started.

Causes of PICU admission were divided into 5 different categories: respiratory insufficiency, neurological insufficiency, heart insufficiency, gastrointestinal/hepatic insufficiency, other causes.

The classification of priority levels has been created by the TIPNET group (Network of Italian PICUs) to identify the patient's need for PICU admission. Priority level is assessed as follows:

- level 1: critical, instable patients in need of intensive treatment and monitoring; no limitation for intensive care;
- level 2: patients in need of intensive monitoring and eventually immediate treatment; no limitation for intensive care;
- level 3: critical, instable patients with low recovery expectations; limited intensive care;
- level 4: non-PICU suitable patients (4a: patients that may not benefit from PICU stay, treatment can be administered in non-intensive care wards; 4b: patients with terminal disease at high risk of mortality).

The pediatric ARDS, if present at PICU admission or during PICU stay, is defined by the PALICC-2 [53].

Patients with sepsis were defined as those with confirmed or suspected infection who had an acute rise in the pSOFA score of 2 points or more from up to 48 hours

before the infection to 24 hours after the infection and who received antimicrobial therapy in the PICU[82].

MOF is defined as a contemporary involvement of 2 or more organs. Organ failures are defined as:

- cardiovascular failure: need for vasoactive amines;
- respiratory failure: need for oxygen therapy or mechanical ventilation;
- neurological failure: Glasgow coma scale score <8;
- gastrointestinal/hepatic failure: total plasma bilirubin >4 mg/dl without the presence of hemolysis or hepatic disease; ALT levels greater than 2 times the upper age limit;
- blood coagulation system failure: altered coagulation with prolonged PT and PTT, INR≥2, platelet count <80.000/mm^3 or platelet reduction of more than 50% compared to the previous 3 days;
- nephro-urinary system: oliguria or anuria, impaired renal function (grade 2 or higher of the KDIGO classification[83],[84]).

The PIM3 (Pediatric Index of Mortality) is a scoring system used to predict the mortality of patients admitted to the PICU. It is calculated on data collected within the first hour after PICU admission[80].

The O-PEWS (Oncological Pediatric Early Warning Score) is a score developed by the Italian Pediatric Onco-Hematology Association (AIEOP) for onco-hematologic patients on the basis of the Pediatric Early Warning Score (PEWS), in order to early identify children in need of PICU admission. It analyses 5 parameters: level of consciousness/behaviour, heart rate, systolic blood pressure, respiratory function, diuresis. Each parameter scores from 0 to 3 points, one extra point is given if the parents or the care giver are concerned, for a maximum of 16 points.

The PELOD score was calculated at first, second and PICU discharge day[85].

3.5 Statistical analysis

The descriptive analysis of the sample is reported using the median and the interquartile range (I-III quartile) for continuous variables and absolute numbers and relative percentages for categorical ones. The study cohort was stratified by solid/non-solid cancer and HSCT/non-HSCTxxa. The presence of statistically significant differences between two groups was assessed using the Kruskal-Wallis test for continuous variables and the $\chi 2$ test for categorical ones.

The associations between patients' characteristics and in-PICU mortality and length of stay were assessed using univariable and multivariable logistic and linear regression models, according to the timing to which the variables refer (pre-PICU and in-PICU). Post-surgical patients who stayed in PICU less than 48 hours were excluded from the analyses.

The statistical significance was set at a p value < 0.05. The analyses were performed using R system, version 4.2.2[(86)].

4. RESULTS

4.1 Overview of the sample

4.1.1 Before PICU admission

Data were collected from a total of 538 patients admitted to 14 Italian PICUs from January 2019 to April 2022 who met the inclusion criteria for our study. Median age was 7 years (IQR 2-12). 54% of admitted children were male, while 46% were female.

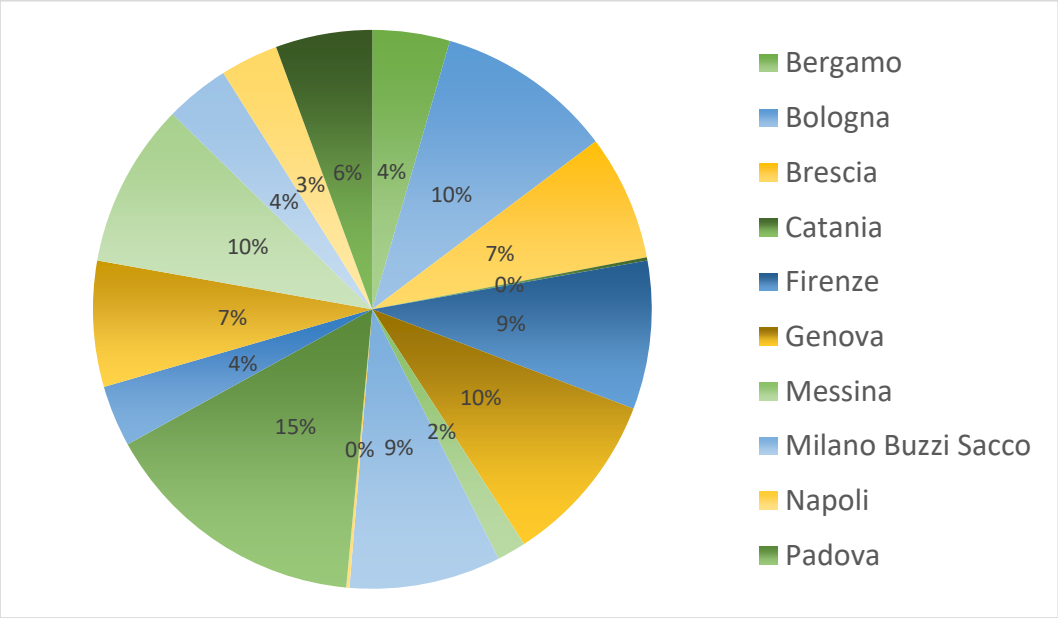

Figure XXIII – Patients' centre of hospitalisation

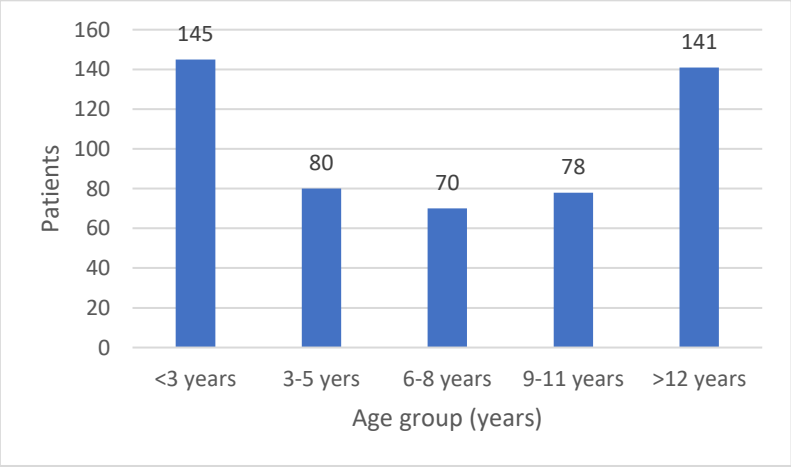

Figure XXIV - Distribution of age groups

The sample includes 454 Caucasian patients (85%), 26 African patients (4,9%), 24 Arabian patients (4,5%), 17 Asian patients (3,2%), 11 Hispanics patients (2,1%), 3 mixed ethnicity patients (0,6%).

Patients' diagnosis is presented in Table 6. Among the 99 (19%) HSCT patients, 53 (54%) underwent allogeneic transplant from related donor, 24 (24%) autologous transplant and 21 (21%) haploidentical related donor transplant. 33 (33%) patients developed GvHD, 12 of grade 1-2 and 21 of grade 3-4. 330 patients had a chronic disease.

Characteristic	Patients=528
Onco-hematologic disease	260 (49%)
HL	6 (1.1%)
LLA	122 (23%)
LMA	33 (6.2%)
NHL	20 (3.8%)
others	79 (15%)
Solid tumor	268 (51%)

Table 6 – Children's diagnosis

Treatment phase	Patients=522
1	237 (45%)
2	93 (18%)
3	192 (37%)

Table 7 - Cases grouped by treatment phase

Children were admitted to the PICUs from the oncology ward of the same hospital (62%), from the oncology ward of another hospital (13%), from the PICU of another hospital (2,1%), from the emergency room (9%) and from other proveniences (2,1%). 209 (41%) patients were admitted post-surgery, among which 84 (16%) stayed in the PICU less than 48 hours.

32% of children were admitted to PICU due to respiratory causes: 6 (2%) patients due to high airway complications, 15 (5%) due to low airways complications, 75 (25%) due to other complications. 70 (23%) patients were admitted to PICU due to neurologic compromise, 25 (8.4%) due to cardiovascular causes, 9 (3%) due to

gastroenterologic causes, 6 (2%) due to renal causes and 92 (31%) due to miscellaneaous causes. 209 (41%) patients were admitted post-surgery, among which 84 (16%) stayed in the PICU less than 48 hours.

180 children received treatment before being admitted to PICU, among which 74 (14%) received HFNC, 23 (4.3%) received NIV, 3 (0.6%) received hemofiltration, 3 (0.6%) received hemodialysis, 28 (5.2%) received vasoactive amines, 60 (11%) received other treatments.

Before PICU admission 101 patients (18%) presented multi organ failure and 44 (19%) developed pARDS.

The median O-PEWS score was 3.0 (0.0,7.0). PIM 3 score median was 2 (1, 8).

Popc score	Patients=500
1	215 (43%)
2	174 (35%)
3	51 (10%)
4	54 (11%)
5	6 (1.2%)

Table 8 - Popc score before PICU admission

4.1.2 PICU stay

Priority level	Patients=502
1	283 (56%)
2	187 (37%)
3	26 (5.2%)
4b	3 (0.6%)

level 1: critical, instable patients in need of intensive treatment and monitoring; no limitation for intensive care; level 2: patients in need of intensive monitoring and eventually immediate treatment; no limitation for intensive care; level 3: critical, instable patients with low recovery expectations; limited intensive care; level 4: non-PICU suitable patients (4b: patients with terminal disease at high risk of mortality)

Table 9 - Cases grouped by priority level

From PICU admission, children stayed in hospital for an average length of 3 days, ranging from a minimum of 0 days to a maximum of 389 days.

The median PELOD score at admission time was 3 (1, 4), at first day of PICU stay 0.6 (0.1, 1.4), at second day of PICU stay 0.3 (0.1, 1.4). The PELOD score at PICU discharge day was 0 (0, 1).

During PICU stay 101 (45%) patients presented multiorgan failure (228 unknown). 186 (35%) patients had respiratory failure, 88 (16%) heart failure, 67 (12%) renal failure and 47 (25%) developed ARDS. 34 patients had a cardiac arrest.

304 (57%) patients underwent medical procedures during PICU stay (Table 11). 161 (33%) children required total parenteral nutrition (TPN).

Medical procedure	Patients=538
IV	235 (45%)
HFNC	120 (22%)
Low flow O_2	22 (4.1%)
Pericardic drainage catheter	4 (0.7%)
Thoracic drainage catheter	31 (5.8%)
Abdominal drainage catheter	14 (2.6%)
Tracheostomy	16 (3%)
Surgery	60 (11%)
Dialysis	40 (7.4%)
ECMO	3 (0.6%)
PIC monitoring	9 (1.7%)
CVC	134 (25%)
Midline	35 (6.5%)
Arterial line	156 (29%)

IV= invasive ventilation; HFNC= high flow nasal cannula; ECMO= extracorporeal membrane oxygenation; PIC= patient-initiated clinics; CVC= central venous catheter

Table 10 - Medical procedures in PICU

96 (18%) patients received NIV, among which 32 (6%) patients received NIV before IT and 43 (8%) received NIV after IT. 235 (45%) patients received IV and 14 (2.6%) received HFOV. Median length of ventilation was 2 days (IRQ 1, 7).

331 (67%) patients required sedation during PICU stay. 277 (51%) children required treatment with curare. During PICU stay 12 children developed abstinence syndrome and 7 developed delirium.

Sedative drug	Patients=538
Morphine	125 (23%)
Fentanyl	134 (25%)
Remifentanil	51 (9.5%)
Sulfentanil	4 (0.7%)
Midazolam	157 (29%)
Dexmedetomidine	157 (29%)
Clonidine	23 (4.3%)
Propofol	98 (18%)
Thiopental	2 (0.4%)
Ketamine	37 (6.9%)

Table 11 - Sedative drugs administered during PICU stay

164 patients (30%) developed an infection during PICU stay. 142 (87%) were treated with antibiotic therapy, 49 (30%) with antiviral therapy and 89 (54%) with antifungal therapy. 50 (30%) patients received only antibiotics, 5 (3%) received antibiotics and antiviral therapy, 42 (25.6%) received antibiotics and antifungal therapy, 43 (26%) received antibiotics, antiviral therapy and antifungal therapy. 67 (12.5%) patients developed a sepsis during the PICU stay.

The majority of children presented a POPC score of 1 and 2 (Table 12).

POPC score	Patients=412
1	153 (37%)
2	148 (36%)
3	72 (17%)
4	34 (8.3%)
5	5 (1.2%)

Table 12 - POPC score at PICU discharge

The majority of death cases were reported during PICU stay (Table 13).

Mortality outcome	Patients=493
In PICU	66 (13%)
After 30 days from PICU discharge	8 (1.6%)
After 90 days from PICU discharge	7 (1.4%)
Total	81 (15%)

Table 13 - Mortality of the overall population of our study

4.1.3 Comparison between solid cancer and non-solid cancer disease

We analysed the subpopulation of hematologic tumor patients compared to solid tumor patients. In our study 268 (49%) children had a diagnosis of solid cancer and 260 (51%) of hematologic cancer. In both solid tumor and hematologic tumor subgroups there was a prevalence of male patients, respectively 53% (141) and 55% (143). Median age was 9 years (3.0, 12.8) for children with solid tumor and 5 years (2.0, 11.0) for children with onco-hematologic disease (p<0.001).

4.1.3.1 Before PICU admission

The majority of hematologic tumor patients were undergoing therapy (treatment phase 1) by the time they were admitted to PICU compared to solid tumor patients, respectively 61% (155) and 31% (82); 18% (47) hematologic tumor patients and 17% (46) solid tumor patients were off therapy (treatment phase 2); the majority of children with solid tumor had not started a therapy (treatment phase 3) by the time of PICU admission compared to liquid tumor patients, respectively 52% (137) and 21% (54). This analysis was significatively different (p<0.001).

99 children were HSCT patients. Hematologic tumor patients underwent HSCT significantly more often (31%) than children with solid tumor (7.5%) (p <0.001).

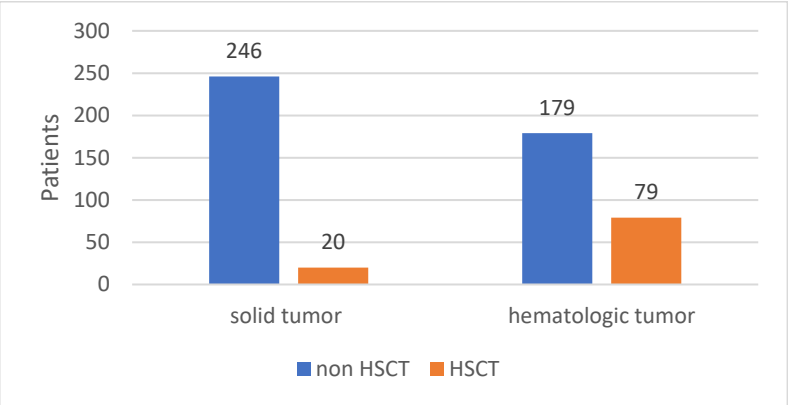

Figure XXV - Transplanted and non-transplanted children by solid and hematologic tumor

Solid tumor patients are more often admitted to PICU from the ward of another hospital (17%) or from another centre (18%) compared to hematologic cancer

patients (respectively, 9.7% and 9.7%). Hematologic tumor patients are more often admitted to PICU from the oncologic ward of the same hospital compared to solid tumor patients (respectively 72% and 52%). This analysis was significatively different ($p<0.001$).

Regarding PICU admission causes, hematologic tumor patients were more often admitted to PICU due to cardiovascular causes ($p<0.001$), miscellaneous causes ($p<0.001$), respiratory low airways causes ($p=0.005$) and other respiratory causes ($p<0.001$) compared to solid tumor patients.

Solid tumor patients presented a lower O-PEWS score compared to hematologic tumor patients, respectively 0.0 (0.0, 3.0) and 6.0 (3.0, 8.0), with a $p<0.001$.

Patients with hematologic cancer presented MOF and pARDS more frequently than patients with solid tumor before admitting PICU (Table 17).

Before PICU admission	Patients=528	**Hematologic tumor** N=260	**Solid tumor** N=268	**p-value**
Multiorgan failure	101 (33%)	87 (45%)	14 (12%)	<0.001
pARDS	43 (19%)	35 (25%)	8 (9.0%)	<0.001

Table 14 - Multiorgan failure (MOF) and pARDS before PICU admission by solid and hematologic tumor

In our sample, 124 (48%) children with hematologic tumor and 47 (18%) children with solid tumor received treatment (HFNC, NIV, dopamine administration, dialysis, other treatments) before PICU admission: this difference is significative ($p<0.001$).

The PIM 2 score and the PIM3 score were significatively different in the two subpopulations.

Score	Patients=474	**Hematologic tumor** N=214	**Solid tumor** N=250	**p-value**
PIM 2	2 (1, 7)	5 (2, 16)	1 (1, 3)	<0.001
PIM3	2 (1, 8)	7 (2, 18)	1 (0, 2)	<0.001

Table 15 - PIM2 and PIM3 score during PICU admission by solid and hematologic tumor

4.1.3.2 PICU stay

29% (75) of children with solid tumor were admitted to PICU after surgery and stayed in PICU less than 48 hours, compared to 3.6% (9) of children with hematologic tumor (p<0.001).

83 (59%) patients with hematologic cancer presented multiorgan failure during PICU stay compared to 18 (22%) patients with solid cancer (p<0.001). Less solid tumor patients presented organ failure (heart, renal, respiratory failure) and pARDS compared to hematologic tumor patients (Table 19 and Table 20).

Organ failure	Patients=528	**Hematologic tumor** N=260	**Solid tumor** N=268	**p-value**
Heart failure	88 (17%)	71 (27%)	17 (6.3%)	<0.001
Renal failure	67 (13%)	62 (24%)	5 (1.9%)	<0.001
Respiratory failure	185 (35%)	122 (47%)	63 (24%)	<0.001

Table 16 - Organ failure by hematologic and solid tumor groups

38 (31%) hematologic tumor patients presented pARDS before PICU admission, compared to 8 (13%) solid tumor patients (p=0.005).

The PELOD score at first day, at second day and at day before PICU discharge was significatively different in the two subgroups (Table 21).

PELOD score	Patients=528	**Hematologic tumor** N=260	**Solid tumor** N=268	**p-value**
Day 1	0.6 (0.1, 1.4)	0.6 (0.2, 2.2)	0.6 (0.1, 0.6)	0.002
Day 2	0.3 (0.1, 1.4)	0.9 (0.2, 3.5)	0.1 (0.1, 0.6)	<0.001
Last day	0 (0, 1)	0 (0, 1)	0 (0, 0)	<0.001

Table 17 - PELOD score by hematologic and solid tumor groups

Among 34 patients who presented cardiac arrest during PICU stay, 25 were hematologic cancer children and 9 were solid cancer children (p<0.001). Total parenteral nutrition was also statistically different: 113 (49%) hematologic tumor patients received it, compared to 48 (19%) solid tumor patients (p<0.001).

Hematologic tumor patients received ventilation for longer periods of time (p<0.001), compared to solid tumor patients, respectively for 5 days (IRQ 2, 10) and for 1 day (IRQ 1, 4).

Ventilation mode	Patients=528	**Hematologic tumor** N=260	**Solid tumor** N=268	**p-value**
NIV	99 (19%)	71 (27%)	28 (10%)	<0.001
IT	235 (45%)	99 (38%)	136 (51%)	0.003

Table 18 – Ventilation modes by hematologic and solid tumor patients

131 (50%) hematologic tumor patients had an infection during PICU stay, compared to 39 (15%) solid tumor patients (p<0.001). 64 (49%) hematologic tumor cancer children developed a sepsis, compared to 4 (11%) solid cancer children (p<0.001).

Hematologic patients had a statistically longer PICU length of stay (5 days) compared to solid tumor patients (2 days) (p<0.001).

Mortality rate during PICU stay was higher for children with hematologic cancer compared to children with solid cancer (Table 19).

Mortality outcome	Patients=528	**Hematologic tumor** N=260	**Solid tumor** N=268	**p-value**
In PICU	66 (13%)	51 (22%)	15 (5.8%)	<0.001
After 30 days from discharge	8 (1.6%)	5 (2.1%)	3 (1.2%)	<0.001
After 90 days from discharge	7 (1.4%)	4 (1.7%)	3 (1.2%)	

Table 19 - Mortality outcome by hematologic and solid tumor

4.1.4 Comparison between transplanted children and non-transplanted children

We analysed the subpopulation of transplanted patients compared to non-transplanted patients. In our study 99 (19%) children underwent HSCT. In both HSCT and non-HSCT subgroups there was a prevalence of male patients. Hispanic children underwent HSCT more often than other ethnic groups (p<0.001).

Ethnic group	Patients=525	**Non-HSCT**	**HSCT**
African	26 (5.0%)	22 (5.2%)	4 (4.0%)
Arabic	24 (4.6%)	20 (4.7%)	4 (4.0%)
Asian	17 (3.2%)	15 (3.5%)	2 (2.0%)
Caucasian	444 (85%)	365 (86%)	79 (80%)
Mixed	3 (0.6%)	2 (0.5%)	1 (1.0%)
Hispanic	11 (2.1%)	2 (0.5%)	9 (9.1%)

Table 20 - Ethnic group by HSCT and non-HSCT subgroups

4.1.4.1 Before PICU admission

The type of tumor has shown a significatively difference among transplanted and non-transplanted children: solid tumors were less represented (p<0.001) (Table 21).

Tumor	Patients=524	**Non-HSCT** N=425	**HSCT** N=99	**p-value**
Onco-hematologic disease	258 (49%)	179 (42%)	79 (80%)	<0.001
HL	6 (1.1%)	3 (0.7%)	3 (3.0%)	
LLA	120 (23%)	79 (19%)	41 (41%)	
LMA	33 (6.3%)	22 (5.2%)	11 (11%)	
NHL	20 (3.8%)	19 (4.5%)	1 (1.0%)	
Others	79 (15%)	56 (13%)	23 (23%)	
Solid tumor	266 (51%)	246 (58%)	20 (20%)	

Table 21 – Children's diagnosis by HSCT and non-HSCT subgroups

The majority of transplanted children were undergoing therapy by the time they were admitted to PICU (53%). A higher percentage of HSCT patients were off therapy compared to non-HSCT patients, respectively 40% and 13%. A higher number of non-HSCT children (43%) had not started a therapy by the time of PICU admission compared to HSCT children (7.2%). This analysis showed a p<0.001.

Non-transplanted children were admitted to PICU from ER (10%), other centres (16%) and ward of another hospital (14%) more often than transplanted children

(respectively 4%, 7.1% and 9.1%). 76% of HSCT patients and 58% of non-HSCT patients were admitted to PICU from the ward of the same hospital. This analysis has shown a p<0.003.

The majority of patients admitted to PICU had a priority level of 1 (67% of HSCT patients and 54% of non-HSCT patients). More non-transplanted children presented a priority level 2 compared to transplanted children, respectively 41% and 21%. 9% of HSCT children had a priority level of 3, compared to 4.1% among non-HSCT children (p=0.002).

Transplanted children were admitted to PICU more often due to respiratory causes compared to non-transplanted children, respectively 35% and 22% (p<0.001). Non-transplanted children were admitted more often due to neurologic compromise compared to transplanted children, respectively 29% and 8.1% (p=0.025).

The O-PEWS score was significatively different between the two subgroups of non-HSCT and HSCT children (p<0.001), respectively 2.0 (0.0, 6.0) and 6.0 (3.0, 9.0).

15% (62) of non-transplanted patients and 39% (39) of transplanted patients presented MOF before PICU admission (p<0.001). 6% (24) of non-HSCT children and 20% (20) of HSCT children were diagnosed with pARDS before PICU admission (p<0.001).

116 (27%) non-transplanted patients and 52 (53%) transplanted patients received treatment (HFNC, NIV, dopamine administration, dialysis, other treatments) before PICU admission, with a significative difference of <0.001.

Transplanted children presented a higher POPC score (grade 3, 4 and 5) compared to non-transplanted children, which presented lower scores (1 and 2).

POPC score	Patients=498	**Non-HSCT** N=409	**HSCT** N=89	**p-value**
1	214 (43%)	190 (46%)	24 (27%)	<0.001
2	173 (35%)	143 (35%)	30 (34%)	
3	51 (10%)	34 (8.3%)	17 (19%)	
4	54 (11%)	38 (9.3%)	16 (18%)	
5	6 (1.2%)	4 (1.0%)	2 (2.2%)	

Table 22 - POPC score before PICU admission by HSCT and non-HSCT subgroups

The PIM 3 score was significatively different in the two subpopulations, with a score of 1 (1, 6) for non-HSCT children compared to a score of 10 (4, 19) for transplanted children (p<0.001).

4.1.4.2 PICU stay

Transplanted children developed multiorgan failure more often than non-transplanted children, respectively 64% (35) and 40% (66) (p=0.002) (Table 23).

Organ failure	Patients=525	**Non-HSCT** N=426	**HSCT** N=99	**p-value**
Heart failure	88 (17%)	57 (13%)	31 (31%)	<0.001
Renal failure	67 (13%)	35 (8.2%)	32 (32%)	<0.001
Respiratory failure	186 (35%)	137 (32%)	49 (49%)	<0.001

Table 23 - Organ failure by transplanted and non-transplanted subgroups

The PELOD score was significatively higher in transplanted children (Table 24).

PELOD score	Patients=525	**Non-HSCT** N=426	**HSCT** N=99	**p-value**
Day 1	0.6 (0.1, 1.4)	0.6 (0.1, 0.9)	1.8 (0.3, 3.5)	<0.001
Day 2	0.3 (0.1, 1.4)	0.3 (0.1, 0.9)	2.2 (0.9, 5.5)	<0.001
Last day	0 (0, 1)	0 (0, 1)	1 (0, 6)	<0.001

Table 24 - PELOD score by transplanted and non-transplanted subgroups

4.7% (19) of non-HSCT patients and 19% (15) of HSCT patients presented cardiac arrest during PICU stay (p<0.001). The need for TPN was significatively different: 57% (47) of HSCT patients received it compared to 28% (114) of non-HSCT patients (p<0.001).

Transplanted children received ventilation for longer periods of time (p<0.001), compared to non-transplanted children, respectively for 7 days (IRQ 2, 16) and 2 days (IRQ 1, 6). Transplanted children received NIV more often compared to non-transplanted patients, respectively 33% and 15% (p<0.001).

47% (47) of transplanted patients and 29% (123) of non-transplanted patients developed an infection during the PICU stay (p<0.001).

The POPC score at time of PICU discharge was assessed higher in transplanted children (p=0.042).

Transplanted patients had a statistically longer PICU length of stay (5 days) compared to non-transplanted patients (3 days) (p=0.012).

Mortality rate was higher for children who underwent HSCT than for non-transplanted children (Table 25).

Mortality outcome	Patients=493	**Non-HSCT** N=409	**HSCT** N=84	**p-value**
In PICU	66 (13%)	36 (8.8%)	30 (36%)	<0.001
After 30 days from discharge	8 (1.6%)	6 (1.5%)	2 (2.4%)	<0.001
After 90 days from discharge	7 (1.4%)	7 (1.7%)	0 (0%)	<0.001
Total	81 (16%)	49 (12%)	32 (38.4%)	

Table 25 - Mortality rate by transplanted and non-transplanted subgroups

4.2 Risk factors

4.2.1 Risk factors for mortality outcome in PICU

We investigated risk factors associated with PICU mortality outcome on a total of 428 patients, excluding post-surgical patients admitted to PICU for less than 48 hours.

Mortality outcome	Patients=407
In PICU	66 (16%)
After 30 days from PICU discharge	8 (2%)
After 90 days from PICU discharge	7 (1.7%)
Total	81 (19%)

Table 26 – Mortality outcome of the population sample, excluding post-surgical patients who stayed in PICU less than 48 hours

4.2.1.1 Univariate analysis

We analysed the mortality outcome during PICU stay for our population of pediatric patients by univariate logistic regression models and multivariate logistic regression models for pre PICU admission predictors and for PICU stay predictors.

The univariate analysis of pre PICU admission shows the following significant predictors: age, hematologic cancer diagnosis, HSCT, infection, multiorgan failure, pARDS, treatment phase, priority dic, O-PEWS score, PIM 3 score, POPC score.

Predictors pre PICU admission	Odds ratios	CI	p-value
Gender	1.12	0.65 – 1.93	NS
Age	1.05	1.01 – 1.11	**0.030**
Hematologic cancer diagnosis	3.10	1.70 – 5.93	**<0.001**
HSCT	5.41	2.95 – 9.92	**<0.001**
Infection	3.10	1.78 – 5.48	**<0.001**
Multiorgan failure	4.50	2.39 – 8.65	**<0.001**
pARDS	2.61	1.16 – 5.75	**0.018**
Treatment phase	0.67	0.48 – 0.91	**0.014**
O-PEWS score	1.31	1.20 – 1.44	**<0.001**
Priority dic (1 and 2 vs 3 and 4b)	0.15	0.06 – 0.39	**<0.001**
PIM 3 score	1.05	1.04 – 1.07	**<0.001**
POPC score	1.85	1.45 – 2.37	**<0.001**

Table 27 - Univariate logistic regression for pre PICU admission predictors

The univariate analysis of PICU stay shows the following significant predictors: multiorgan failure, respiratory failure, heart failure, renal failure, cardiac arrest, TPN and NIV.

Predictors PICU stay	Odds ratios	CI	p-value
Multiorgan failure in PICU	6.74	3.23 – 15.27	**<0.001**
pARDS in PICU	1.27	0.59 – 2.66	NS
Respiratory failure	5.19	2.87 – 9.83	**<0.001**
Heart failure	7.83	4.37 – 14.25	**<0.001**
Renal failure	6.52	3.51 – 12.16	**<0.001**
Cardiac arrest	173.71	49.26 – 1107.41	**<0.001**
TPN	3.06	1.75 – 5.44	**<0.001**
Sepsis	1.93	0.91 – 4.14	NS
Ventilation	1.77	0.47 – 11.54	NS
NIV and/or IV length	1.01	0.99 – 1.03	NS
NIV	2.04	1.07 – 3.90	**0.030**
IT	0.99	0.47 – 2.25	NS
Length of stay	1.00	0.99 – 1.01	NS

Table 28 - Univariate logistic regression for PICU stay predictors

4.2.1.2 Multivariate analysis

The multivariate analysis of pre PICU admission shows a significant value for: HSCT, O-PEWS score, priority dic and PIM 3 score.

Predictors pre PICU admission	Odds ratios	CI	p-value
HSCT	3.10	1.26 – 7.59	**0.013**
O-PEWS score	1.18	1.04 – 1.34	**0.010**
Priority dic (1 and 2 vs 3 and 4b)	0.19	0.05 – 0.69	**0.012**
PIM 3 score	1.04	1.02 – 1.07	**<0.001**
Age	1.05	0.97 – 1.15	NS
Hematologic tumor	0.81	0.28 – 2.44	NS
POPC score	1.39	0.97 – 2.00	NS

Table 29 - Multivariate logistic regression for pre PICU admission predictors

The multivariate analysis of PICU stay shows a significant value for: multiorgan failure and cardiac arrest.

Predictors PICU stay	Odds ratios	CI	p-value
Multiorgan failure	6.29	1.90 – 23.85	**0.004**
Cardiac arrest	54.47	8.87 – 1098.43	**<0.001**
TPN	0.67	0.21 – 2.08	NS
Infection	2.19	0.70 – 7.41	NS
IT	1.46	0.38 – 6.40	NS
NIV	0.39	0.12 – 1.24	NS

Table 30 - Multivariate logistic regression for PICU stay predictors

4.2.2 Risk factors for PICU length of stay

4.2.2.1 Univariate analysis

We investigated risk factors associated with PICU length of stay outcome on a total of 428 patients, excluding post-surgical patients admitted to PICU for less than 48 hours. The median length of stay of the population sample was 4 days. Hematologic tumor patients and transplanted patients presented a longer length of PICU stay, respectively 5 (2, 13) and 6 (3, 18), compared to solid tumor patients and non-transplanted patients. We analysed the length of PICU stay outcome for our population of pediatric patients by univariate logistic regression models and multivariate logistic regression models for pre PICU admission predictors and for PICU stay predictors.

The univariate analysis of pre PICU admission shows the following significant predictors: hematologic tumor diagnosis, infection, O-PEWS score, priority level 2, multiorgan failure, pARDS and PIM 3 score.

Predictors pre PICU admission	**Estimates**	**CI**	**p-value**
Gender	0.10	-1.86 – 2.06	NS
Age	0.03	-0.15 – 0.20	NS
Hematologic tumor diagnosis	2.94	0.99 – 4.89	**0.003**
HSCT	2.57	-0.08 – 5.23	NS
Infection	4.85	2.89 – 6.80	**<0.001**
Treatment phase	-0.40	-1.48 – 0.68	NS
O-PEWS score	0.51	0.19 – 0.83	**0.002**
Priority level 2	-3.50	5.55 – 1.45	**0.001**
Priority dic	2.13	-2.42 – 6.68	NS
Multiorgan failure	4.67	1.91 – 7.42	**0.001**
pARDS	5.02	0.79 – 9.24	**0.020**

POPC score	0.58	-0.38 – 1.55	NS
PIM 3 score	0.08	0.02 – 0.14	**0.007**

Table 31 - Univariate logistic regression models for pre PICU admission predictors

The univariate analysis of PICU stay shows the following significant predictors: pARDS, multiorgan failure, respiratory failure, heart failure, renal failure, NIV, non-invasive and/or invasive ventilation length, TPN.

Predictors PICU stay	**Estimates**	**CI**	**p-value**
pARDS	4.21	0.13 – 8.29	**0.043**
Multiorgan failure	3.42	0.22 – 6.62	**0.036**
Respiratory failure	5.44	3.53 – 7.36	**<0.001**
Heart failure	3.56	1.18 – 5.94	**0.003**
Renal failure	7.34	4.68 – 10.00	**<0.001**
Ventilation	5.07	-0.77 – 10.91	NS
NIV and/or IV length	0.78	0.66 – 0.91	**<0.001**
NIV	4.33	1.41 – 7.25	**0.004**
IT	3.19	-0.34 – 6.72	NS
Cardiac arrest	0.94	-2.50 – 4.38	NS
TPN	7.44	5.53 – 9.34	**<0.001**
Sepsis	-3.31	-7.37 – 0.75	NS

Table 32 - Univariate logistic regression for PICU stay predictors

4.2.2.2. Multivariate analysis

The multivariate analysis of pre PICU admission shows a significant value for multiorgan failure.

Predictors pre PICU admission	Estimates	CI	p-value
Multiorgan failure	4.91	0.03 – 9.80	**0.049**
Age	0.10	-0.26 – 0.47	NS
Hematologic tumor	-0.23	-4.64 – 4.17	NS
HSCT	1.84	-2.58 – 6.27	NS
O-PEWS score	-0.03	-0.66 – 0.60	NS
PIM 3 score	0.01	-0.11 – 0.13	NS
POPC score	0.64	-1.17 – 2.44	NS
Priority dic	4.20	-2.75 – 11.14	NS

Table 33 - Multivariate logistic regression for pre PICU admission predictors

The multivariate analysis of PICU stay shows a significant value for non-invasive and/or invasive ventilation length and TPN. Modello 6

Predictors PICU stay	Estimates	CI	p-value
NIV and/or IV length	0.67	0.53 – 0.81	**<0.001**
TPN	3.74	1.19 – 6.29	**0.004**
Infection	1.81	-0.76 – 4.39	NS
Respiratory failure	-0.36	-2.89 – 2.18	NS
Cardiac failure	-2.39	-5.42 – 0.65	NS
Renal failure	2.82	-0.85 – 6.49	NS

Table 34 - Multivariate logistic regression for PICU stay predictors

5. DISCUSSION

In the past few decades, big improvements have been made in the field of pediatric oncology thanks to more aggressive and efficient treatment protocols, deeper understanding of cancer biology and advancements in the hematopoietic stem cell transplantation, which have led to better outcomes for children with cancer. Despite these advances, pediatric oncology patients may require admission to the intensive care unit due to the complexities of their disease and treatment-related complications. However, recent studies are lacking in literature. To date the majority of available data are derived from small, single-center retrospective studies, which have provided valuable insights but on a limited scale. In view of the limitations of the existing literature, this work aims at bridging this gap and contributing at valuable information to address further research.

5.1 Mortality

5.1.1 Mortality in the overall population sample

Oncologic children admitted to PICU are a high risk population due to the numerous complications that may arise as a consequence of the underlying disease, cancer therapies and immunosuppression. Recent studies report that about 14% of HSCT patients require PICU admission[37],[22]. Accordingly to literature, the most common causes of PICU admission in our study were respiratory and neurologic failure[1],[21],[22],[27],[43],[87],[88],[41],[89],[90]. The mortality rate of these patients is reported to be higher compared to the general PICU population mortality, which ranges approximately between 2.5% and 5% [91],[21]. In our study, the overall mortality rate in PICU was 13%, as also reported in a study by *Dalton et al* [89]. Other studies show higher mortality rates ranging from 22% to 51%[1],[37], [92], [43], [92], [93], [94], [95], [87], [96]. In a study from *Zinter et al* mortality rate was assessed lower (6.8%)[35]. A meta-analysis from 2022 including 31 similar studies has shown a pooled PICU mortality rate of 27.8%[97]. When post-surgical patients admitted to PICU for less than 48 hours were excluded from our analysis, PICU mortality increased to 16%, compared to 33% reported by *Woesten-van Asperen et al*(97). The different mortality rates could be due to the heterogeneity of inclusion and exclusion criteria of the different studies, as also *Woesten-van Asperen et al* noted.

This limits the comparability of the studies and brings to light the need for a consensus on PICU admission criteria guidelines.

5.1.2 Mortality in the HSCT population sample

Patients who had received HSCT were overall more at risk for complications and poorer outcome than non-transplanted patients: they presented higher priority level at PICU admission, as well as higher O-PEWS score, POPC score, PELOD score and PIM 3 score. They also presented multiorgan failure more often and received more often respiratory and cardiovascular support both before and during PICU stay compared to non-HCST patients. This shows that, despite the fact that HSCT is a successful treatment for oncologic patients, transplanted children may develop severe complications. However, from our analysis, transplanted patients admitted to PICU had lower mortality (36%) compared to literature. Studies report mortality rates ranging from 37% to 60% for HSCT patients discharged from PICU[27],[38],[40],[98],[99],[100],[101],[102],[25]. A meta-regression analysis from *van Gestel et al* in 2008(36) showed an overall intensive care unit mortality for HSCT children of 60% (range, 25%-91%). In a study conducted in Padua's PICU in 2017 90-days mortality was assessed at 65.7%[22], as also reported by *Afessa* in 2010[103] (65%). *Zinter et al*[35] found a low mortality rate of 16.2% for pediatric patients who underwent HSCT admitted to PICU, although a decreased admission illness severity was reported by the authors.

5.2 Risk factors

Studies in literature usually focus on outcomes related to underlying disease or treatments received in PICU, such as ventilatory, hemodynamic or renal support. Interestingly, to date no other work except ours has taken into consideration the whole clinical course of the patient before and during PICU admission, from diagnosis to organ functionality, to therapy and procedures, to outcomes. Having collected both before PICU admission and during PICU stay data has enabled us to analyse pre-PICU admission and PICU stay risk factors related to mortality and length of PICU stay.

5.2.1 Risk factors for PICU mortality outcome

As second objective of our study we analysed risk factors associated with mortality outcome. Before PICU admission variables associated with negative outcome in PICU in the univariate analysis were: age, hematologic cancer diagnosis, HSCT, infection, treatment phase, multiorgan failure, pARDS, priority levels 1 and 2, PIM 3 score, POPC score and O-PEWS score. In the univariate analysis of our study, hematologic cancer diagnosis was related to higher PICU mortality, accordingly to other studies[95],[35], while *Dursun et al*[96] reported no difference. However, the type of cancer is no longer significatively different in the multivariate analysis. A history of HSCT showed to be a risk factor for PICU death in univariate analysis ($p<0.001$), accordingly to other studies[37],[22],[36], and in multivariate analysis ($p=0.038$), unlike *Pechlaner et al*[37]. The presence of multiorgan failure or pARDS at PICU admission time was related to increased PICU mortality in our analysis, as well as in other studies[22],[37],[1]. Accordingly to *Zinter et al,* that reports 22.2% mortality in children with infection and 11.1% in children without infection[35], infection is associated to higher mortality (odds ratio 3.10). The PIM 3 score proved to be a good predictive score for mortality, as reported by *Straney et al*[80]. The POPC score could be used not only to assess the patient's performance but also as a mortality predictive score. Further validation would be necessary.

Our study shows the efficacy of the O-PEWS score developed by the Italian Pediatric Onco-Hematology Association (AIEOP) in the pediatric oncologic population admitted to PICU. The use of the O-PEWS score in our study has proven to be valuable at assessing severity of illness and at predicting mortality in critically ill children. In our study the median O-PEWS score was 3 (0.0, 7.0) and became 4 (1.0, 7.0) when post-surgical patients admitted to PICU for less than 48 hours were excluded. Hematologic tumor patients and HSCT patients presented higher scores, respectively 6 (3.0, 8.0) and 6 (3.0, 9.0), which reflects the higher morbidity and mortality of these two population subgroups. It is important to emphasize that the O-PEWS score evaluates diuresis in addition to the other considered variables. Therefore, compared to other previous versions of the PEWS score, it provides essential information about the patient's renal function. Hence, this work could be considered as a starting point for further validation of the O-PEWS.

The univariate analysis for PICU stay variables showed association with PICU mortality for presence of multiorgan failure during PICU stay, respiratory, cardiac and renal failure, NIV, cardiac arrest and TPN. Interestingly, 101 patients were admitted with MOF and 44 with pARDS but no patients developed MOF during PICU stay and only 3 developed pARDS, more likely due to prolonged ventilatory support. This data suggest that PICU treatments are appropriate and efficient. According to literature, MOF is associated with poorer outcomes[43],[92],[95],[87],[96],[104],[105]. The PELOD score may be used to assess organ failure severity and to predict mortality.

Renal failure has been associated with negative outcome in the intensive care unit not only in onco-hematologic patients[43],[1], but also in patients with non-oncologic disease[106]. Studies[43],[104] report better outcome for patients with renal failure at admission time compared to those who develop it during PICU stay. This may be due to the different etiology of renal failure: tumor lysis syndrome is the most frequent cause before admission, while the development of renal failure during PICU stay is related to multiorgan failure and hemodynamic instability. In our study only 6 (2%) patients were admitted to PICU due to renal causes; during PICU stay 67 (12%) children developed renal failure, mostly due to multiorgan failure, hemodynamic instability and sepsis. In our work, the presence of renal failure was associated with higher mortality in the univariate analysis for PICU stay risk factors; PICU length of stay was related to presence of renal failure during PICU stay, as reported in our univariate analysis for length of stay risk factors. The study from *Pillon et al* showed significatively higher mortality in both univariate and multivariate analysis for AKI present at PICU admission and during PICU stay[1].

In the multivariate analysis for pre PICU admission predictors HSCT ($p=0.038$), priority levels 1 and 2 ($p=0.015$), O-PEWS score ($p=0.017$) and PIM 3 score ($p<0.001$) were associated with higher mortality in PICU. In the multivariate analysis for PICU stay predictors multiorgan failure ($p=0.004$) and cardiac arrest ($p<0.001$) were confirmed significatively associated to PICU mortality. 31 (91%) among 34 children who presented cardiac arrest died in PICU. Also *Pillon et al* reported in 2019 higher mortality rates in case of cardiac arrest ($p=0.007$) in their multivariate analysis for predictors of 90-day mortality[1].

5.2.2 Risk factors for PICU length of stay outcome

As secondary objective our study also focuses on risk factors associated with length of PICU stay. From the univariate analysis children with hematologic tumor diagnosis, infection, higher O-PEWS score and PIM 3 score, priority level 2, multiorgan failure and pARDS before PICU admission stayed in PICU significantly longer. PICU stay predictors associated with length of stay resulted pARDS, multiorgan failure, respiratory failure, heart failure, renal failure, NIV, non-invasive and/or invasive ventilation length, TPN. Interestingly, these predictors were also significative in the univariate analyses for mortality outcome. In the multivariate analysis, multiorgan failure ($p=0.049$) as pre PICU predictor and non-invasive/invasive ventilation length ($p<0.001$) and TPN ($p=0.004$) as PICU predictors were associated with longer PICU stay. Providing the right respiratory support treatment with adequate timing from the beginning of PICU stay while avoiding delayed escalation of treatment has proven to be a key point to shorten PICU length of stay and therefore minimize its complications. Moreover, an increasingly tight cooperation between onco-hematologists and intensivists is also needed and recommended. Further studies should focus on the development of up-to-date guidelines to offer a personalized and effective approach based on the patient's characteristics and needs to ensure the best quality of care.

5.3 Appropriateness and timing of intensive care treatment

The higher survival of our cohort compared to previous studies may be related to deeper knowledge and significant improvements in PICU care, such as the use of early warning score (PEWS) to identify patients in need of PICU admission, the better timing of PICU admission and therapy administration, the more appropriate ventilation treatment for children at high risk of severe respiratory failure, the introduction of lung-protective ventilation[65]. It is important to notice that the onco-hematology wards in our study were sufficiently equipped and qualified to provide to unstable patients support therapies, such as NIV, HFNC, dialysis and amine infusion, differently from previous studies. It is therefore possible that the population admitted to PICU has been negatively selected and that only the most critically ill children with potentially poorer prognose have received intensive care treatment. However, the lower mortality rates of our study compared to literature suggest that a successful cooperation between oncology wards and PICUs has been

developed. Our work shows great quality and appropriateness of care for oncologic children in Italian oncology wards and PICUs settings.

5.3.1 Ventilatory treatment

One of the main questions in the field of intensive care is the ideal timing of intubation and invasive mechanical ventilation procedures. In our population invasive mechanical ventilation (IMV or IV) was not significatively associated with PICU mortality outcome, unlike in previous studies. Literature reports poor outcomes for mechanically ventilated children[37],[22] with survival rates ranging from 25%[27],[100],[107] to 42,5% [35], to 48%[100], to 58%[25],[38]. In most studies invasive mechanical ventilation was delayed as long as possible to avoid IV complications. The use of NIV was rather preferred. It is therefore possible that patients with severe respiratory failure may be transferred too late to PICU or received delayed intubation after NIV failed attempt. Delayed intubation after PICU admission may be associated with an increased risk of mortality[40]: *Rowan et al* showed that children who received delayed intubation after 4 days of PICU stay presented higher mortality. Studies on adult populations suggest that the time between intensive care admission and intubation may have a strong predictive value on outcome[108] and that early intubation may improve survival rates[109],[110]. Furthermore, *Rowan et al* reported higher mortality rates for children placed on NIV before intubation than for those who were intubated without prior NIV attempt. These results are similar to the study from *van Gestel et al* (100) and to our findings: 32 patients received NIV prior to intubation (IT) and 16 of them died (50%); among 190 children receiving IT without prior NIV attempt 22 patients (11.6%) died in PICU. Further research should focus on the development of early warning scores to predict NIV failure in order to early identify children at higher risk of severe respiratory failure, recognize patients that would benefit from invasive mechanical ventilation and provide guidelines for ideal modality and timing of intensive care ventilatory treatment to avoid delayed escalation from NIV to uncomplicated intubation and IV.

5.3.2 ECMO treatment

In the past few years numerous studies have focused on ECMO treatment in oncologic patients. Some studies report improving outcomes even for oncologic

HSCT children receiving ECMO treatment in PICU[111],[112]. However, *Suzuki et al* showed that, despite the use of ECMO has expanded over the latest two decades (2000-2019), mortality in children with neoplasm has remained unchanged[113]. Unfortunately, the results of our study suggest that survival rates are not increasing, accordingly to *Maue et al*[114] and to a study on an adult population by *Pravin et al*[115]. 3 out of 3 patients that received ECMO in our study died within PICU stay. Moreover, oncologic patients have shown to be more susceptible to infections while on ECMO compared to the general ECMO population, although the prognostic impact of these infections was minimal. Thus, ECMO should not be withheld in oncologic patients solely with concern for infection[116]. However, further research on the appropriateness and timing of ECMO support for oncologic transplanted and non-transplanted children is needed to improve intensive care treatment and outcomes in this high risk population.

5.4 Strengths and limitations of our study

Our study presents several strengths. First of all, this study addresses a substantial gap in the existing literature. Most recent studies date back to 2012-2014 and just a few were published in recent years[22],[1],[97],[37]. Our work discloses important updates, providing contemporary insights into critical care for pediatric oncologic patients. Differently from most studies, our multicentre work reflects the experience of 14 different centres representative of different areas and regions of Italy and may be therefore of great international interest. Thanks to the prospective phase of the study, our work presents fewer sources of bias and confounding compared to most previous studies, which presented a retrospective design. The big sample of patients requiring PICU admission and the inclusion of solid and non-solid tumor patients as well as transplanted and non-transplanted patients in our population enabled us to perform strong statistics and a reliable inference for the whole oncologic PICU population. Moreover, our study not only focuses on PICU procedures and treatments but also gives valuable insights onto a wide set of pre-PICU admission variables and scores that may influence patient's outcomes as well. Early recognising high risk patients and predicting their outcomes may help in the decision-making process regarding timing of PICU admission and appropriateness of medical procedures. It also may have an impact on an ethic level and in the relationship between clinicians and the patients' families. The limitations of our

study are its partially retrospective design, its missing data and its relatively short period of time. However, data collection has continued after the time of our study and updates will be analysed. Nevertheless, our multicenter work contributes to enrich literature with relevant data about the high-risk population of pediatric oncologic patients admitted to PICU and provides important insights onto the current quality of care in Italian PICUs.

6. CONCLUSIONS

In conclusion, our study describes the population of pediatric oncologic patients admitted to PICU as well as its outcomes and risk factors. Patients with hematologic tumor diagnosis and children who underwent hematologic stem cell transplantation present higher risk factors and poorer outcomes, requiring great attention. PIM 3 score, O-PEWS score, priority level and a history of HSCT may be important information and tools to be used in the oncology ward in order to recognize patients at higher risk of mortality, that should be early admitted to PICU to receive the most adequate treatments. Moreover, PICU procedures should firstly address multiorgan failure and avoid cardiac arrest, as they have shown to be the main predictors of mortality in admitted children. Our study also presents the O-PEWS score developed by Italian Pediatric Onco-Hematology Association (AIEOP) as a valuable score to predict need of PICU admission and mortality rates. Our work supports clinical decision-making and encourages cooperation between the onco-hematology wards and the PICUs in order to enhance survival rates in this patients' population.

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