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Systemic Review

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Differential Diagnosis of Acute Liver Failure in Children: A Systematic Review

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: To develop a probability-based differential diagnosis for pediatric acute liver failure (PALF) based on age and socioeconomic status of the country of origin.
Methods: Comprehensive literature search using PubMed, EMBASE, and SCOPUS databases was performed. Children 0–22 years of age who met PALF registry criteria were included. Articles included >10 children, and could not be a case report, review article, or editorial. No language filter was utilized, but an English abstract was required. Etiology of PALF, age of child, and country of origin was extracted from included articles.
Results: 32 full text articles were reviewed in detail; 2,982 children were included. The top diagnosis of PALF in developed countries was acetaminophen toxicity (9.24%; 95% CredI 7.99–10.6), whereas in developing countries it was Hepatitis A (28.9%; 95% CredI 26.3–31.7). In developed countries, the leading diagnosis of PALF in children aged <1 year was metabolic disorder (17.2%; 95% CredI 10.3–25.5), whereas in developing countries it was unspecified infection (39.3%; CredI 27.6–51.8). In developed countries, the leading diagnosis in children aged >1 year was Non-A-B-C Hepatitis (8.18%; CredI 5.28–11.7), whereas in developing countries it was Hepatitis A (32.4%; CredI 28.6–36.3).
Conclusion: The leading causes of PALF in children aged 0-22 years differ depending on the age and developmental status of their country of origin, suggesting that these factors must be considered in the evaluation of children with PALF.

Keywords: Acute liver failure; Pediatric; Developed countries; Developing countries; Systematic review

INTRODUCTION

Pediatric acute liver failure (PALF) is a rapidly progressive syndrome in children that can lead to many devastating complications, such as renal and/or respiratory failure, hemodynamic instability, cerebral edema, sepsis, coagulopathy, and aplastic anemia [1-4]. The incidence of acute liver failure (ALF) across all age groups in the developed world is rare with an incidence of 10 cases per million. In the United States, it is estimated that 1,600 cases of ALF are reported each year [5]. In developing countries, the exact incidence of ALF is unknown, but estimated to be higher due to increased rates of hepatotropic infection [6].

The PALF registry developed criteria to classify PALF, which are distinct from those that define ALF in the adult population [7]. It is also important to distinguish PALF from acute liver injury in a child with pre-existing liver disease (i.e., acute on chronic liver failure) [8]. As such, the most updated definition of PALF requires the absence of identified pre-existing liver disease within the preceding 8 weeks of presentation, coagulopathy not corrected by administration of Vitamin K, evidence of hepatocellular injury, and either: international normalized ratio (INR) ≥1.5 with evidence of encephalopathy or INR ≥2.0 with or without evidence of encephalopathy [7].

It is estimated that 38 percent of cases of PALF have an unknown etiology, and the remaining causes of PALF can be classified as infectious, immunologic, metabolic, ischemic, and toxin- or drug-related, which differ depending on age group and geographic region [5]. The goal of this systematic review was to determine a probability-based differential diagnosis of the etiologies of PALF, taking into account the age of the child and expected variations related to geographic location.

MATERIALS AND METHODS

This systematic review followed The Preferred Reporting Items in Systematic Reviews and Meta-Analysis guidelines [9].

Literature search

A comprehensive literature search was performed using the PubMed, EMBASE, and SCOPUS databases. The search terms, "Acute Liver Failure" AND "Children" were input. Case reports, review articles, and studies including less than 10 children were excluded. In the SCOPUS search engine, the publication date was filtered to include only articles published in 2017, 2018, or 2019. No date filter was used in the PubMed or EMBASE databases. The aforementioned literature search was performed by two authors on two separate occasions (December 2018 and November 2019) to obtain the most complete review of the current literature. The bibliographies from each of the search engines were uploaded into the RefWorks program and exact duplicates were excluded automatically. The remaining articles were uploaded into Rayyan QCRI application [10]. In the Rayyan application, remaining duplicates were removed by hand and the abstracts were reviewed by two authors separately to include only those that met inclusion criteria (**Table 1**) [7]. Any conflicting decisions were resolved by a third author. Bibliographies of relevant review articles identified through the initial search were reviewed for studies that could qualify for this review. Full-text articles were reviewed for inclusion and

Table 1. Inclusion and exclusion criteria

I. Title contains "Acute Liver Failure" or "Acute Hepatic Failure"
II. Minimum number of studied children is 10
III. Children are age 0–22 years old
IV. Diagnosis of PALF was made according to the PALF registry criteria [7]
V. Study entry criteria requires review of all children with ALF without another co-existing diagnosis or treatment modality. For example, studies that examined the etiology of acute liver failure from only children with known metabolic diseases were excluded. Studies that examined the etiology of acute liver failure from only children who underwent liver transplant were excluded.
VI. Not a case report
VII. Not a review article
VIII. Not an editorial
IX. No language filter was utilized, but an English abstract was required

PALF: pediatric acute liver failure, ALF: acute liver failure.

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exclusion criteria. When articles used the same or mostly overlapping cohort of children in their analysis, only the most recently published article was included.

Data extraction

The selected articles were read individually, and data from each was extracted into Google spreadsheets. The country of origin for each study was identified and countries were divided into "developed" and "developing" categories as identified by the United Nations [11,12]. Etiologies of PALF and number of children affected with each were recorded. When possible, specific ages of the patients were recorded. For missing or unclear data, we contacted the authors of the articles by email.

Data analysis

A Bayesian methodology was employed to determine the rate estimates and the associated 95% credible intervals for each disease entity; the beta distribution was used as the conjugate prior to the conditional likelihood distribution for each rate estimate determined from the extracted data [11,13].

RESULTS

Fig. 1 outlines the results of the systematic review. The database searches provided a total of 1,152 results (PubMed- 778 articles, EMBASE- 283 articles, Scopus- 91 articles). In addition, bibliography reviews provided 2 more studies.

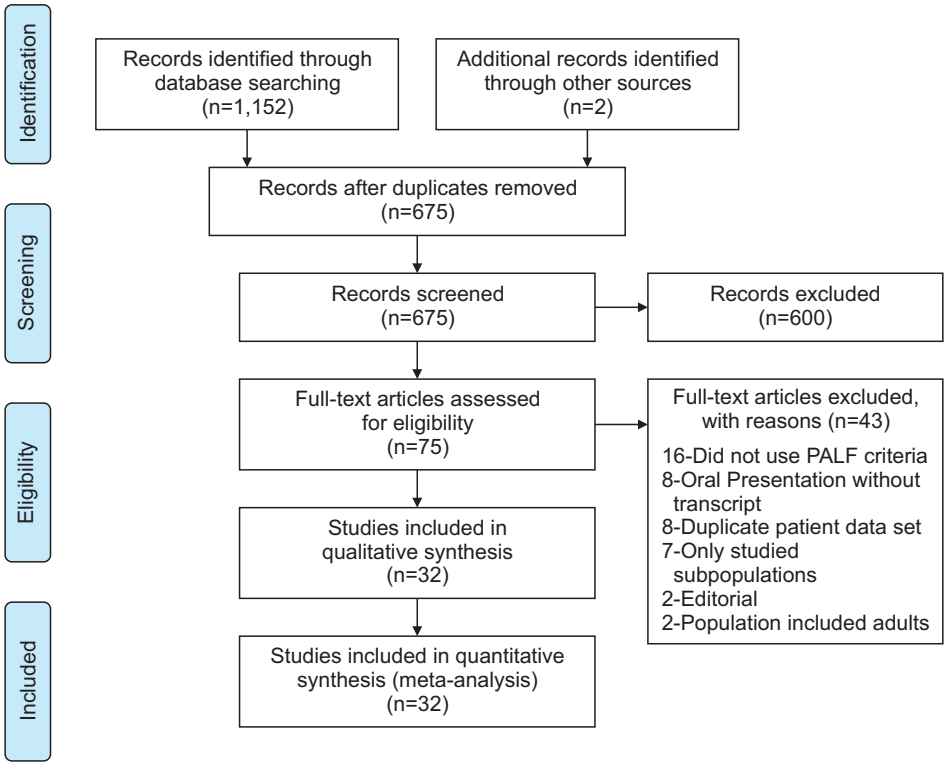

Fig. 1. Literature search results. Adapted from Moher et al. (PLoS Med 2009;6:e1000097).

After exact duplicates were removed, abstracts of 675 articles were reviewed. After exclusion of abstracts that did not meet inclusion criteria (**Table 1**) [7], a total of 75 full-text articles were examined in detail. Forty-three full text articles were excluded: 16 did not utilize PALF criteria, 8 were oral presentations without full length transcripts (including abstracts presented at conferences), 8 utilized data from the same or mostly overlapping cohort of patients, 7 examined sub-populations (ex, children receiving liver transplants), 2 were editorials, and 2 did not differentiate between adults and children in their data reports.

A total of 32 articles (published between 1997–2019) met inclusion criteria and were analyzed for this study. **Table 2** [14-45] summarizes the data extracted from these studies. A total of 2,989 subjects were included in our analysis (2,019 from developed countries and 970 from developing countries), with an age range of 0–22 years old.

Table 3 shows the most common diagnoses of PALF in both developed and developing countries. Of the 2,019 children in developed countries, the most frequent cause of PALF was acetaminophen toxicity (9.24%; 95% CredI 7.99–10.6), followed by unspecified metabolic disorders (5.47%; 95% CredI 4.5–6.52), and unspecified infection (5.06%; 95% CredI 4.13–6.08). 39.7% (95% CredI 37.6–41.9) of the causes were of indeterminate origin. Of the 970 children in developing countries, the most frequent cause of PALF was Hepatitis A (28.9%;

Table 2. Article extraction

First author	Year published	Study design	Country	Economic status	No. of patients	Percentage of total patients (%)*
Alam [14]	2015	Retrospective	India	Developing	30	1.0
Alam [15]	2016	Prospective	India	Developing	33	1.1
Baris [16]	2012	Retrospective	Turkey	Developing	74	2.5
Bersani [17]	2019	Retrospective	Italy	Developed	10	0.3
Brett [18]	2013	Retrospective	Portugal	Developed	28	0.9
Chongsrisawat [19]	2009	Retrospective	Thailand	Developing	53	1.8
Di Giorgio [20]	2019	Retrospective	Italy	Developed	56	1.9
Di Giorgio [21]	2017	Retrospective	Italy	Developed	55	1.8
Gilbert Perez [22]	2018	Retrospective	Spain	Developed	49	1.6
Grama [23]	2019	Retrospective	Romania	Developing	97	3.2
Hegarty [24]	2013	Retrospective	UK	Developed	127	4.2
Kathemann [25]	2015	Retrospective	Germany	Developed	37	1.2
Kaur [26]	2013	Prospective	India	Developing	43	1.4
Lee [27]	2018	Retrospective	Argentina	Developing	210	7.0
Lu [28]	2009	Prospective	USA	Developed	53	1.8
Mazumder [29]	2016	Retrospective	Bangladesh	Developing	62	0.2
Mckiernan [30]	2016	Retrospective	UK	Developed	39	1.3
Mustafa [31]	2009	Retrospective	UK	Developed	56	1.9
Narkewicz [32]	2018	Prospective	USA and UK	Developed	1,144	38.3
Ng [33]	2016	Retrospective and prospective	Malaysia	Developing	60	2.0
Nunez-Ramos [34]	2018	Retrospective	Spain	Developed	20	0.1
Oh [35]	2016	Retrospective	Korea	Developed	126	4.2
Ozcay [36]	2011	Retrospective	Turkey	Developing	67	2.2
Ozcay [37]	2016	Retrospective	Turkey	Developing	91	3.0
Rajanayagam [38]	2013	Retrospective	Australia	Developed	54	1.8
Rivera-Penera [39]	1997	Retrospective	USA	Developed	66	2.2
Sanchez [40]	2016	Retrospective	Argentina	Developing	57	1.9
Sanchez [41]	2012	Retrospective	Argentina	Developing	40	1.3
Silverio [42]	2015	Prospective	Cuba	Developing	31	1.0
Tung [43]	2000	Retrospective	London	Developed	75	2.5
Wands [44]	2018	Retrospective	Scotland	Developed	24	0.8
Yankol [45]	2016	Retrospective	Turkey	Developing	22	0.7

*Rounded to nearest 0.1%.

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Table 3. Etiology of PALF in children 0-22 years old in developed and developing countries

Etiology*	Developed (n=2,019)	Mean	95% credible interval		Etiology†	Developing (n=970)	Mean	95% credible interval	
			Lower	Upper				Lower	Upper
Indeterminate	770	39.7	37.6	41.9	Hepatitis A	316	28.9	26.3	31.7
Acetaminophen toxicity	179	9.24	7.99	10.6	Indeterminate	220	20.1	17.8	22.6
Unspecified metabolic disorder	106	5.47	4.5	6.52	Unspecified infection	104	9.52	7.86	11.3
Unspecified infection	98	5.06	4.13	6.08	Wilson's disease	85	7.78	6.27	9.44
Other	79	4.08	3.24	5	Autoimmune disorder	48	4.4	3.26	5.69
Ischemia	67	3.46	2.69	4.31	Unspecified toxin	30	2.75	1.86	3.8
Unspecified toxin	64	3.3	2.55	4.14	Dengue virus	29	2.66	1.79	3.69
Hemophagocytic lymphohistiocytosis	55	2.84	2.15	3.62	Unspecified metabolic disorder	29	2.66	1.79	3.69
Herpes simplex virus+enterovirus co-infection	53	2.73	2.06	3.51	Hemophagocytic lymphohistiocytosis	28	2.56	1.71	3.58
Wilson's disease	51	2.63	1.97	3.39	Acetaminophen toxicity	27	2.47	1.64	3.47
Congenital heart disease	43	2.22	1.61	2.92	Mushroom toxicity	19	1.74	1.05	2.6
Galactosemia	39	2.01	1.44	2.68	Hepatitis B	11	1.01	0.504	1.68
Hemochromatosis	31	1.6	1.09	2.2	Galactosemia	11	1.01	0.504	1.68
Autoimmune disorder	30	1.55	1.05	2.14	Albendazole toxicity	11	1.01	0.504	1.98
Non-A-B-C hepatitis	23	1.19	0.754	1.71					
Herpes simplex virus	23	1.19	0.754	1.71					
Unspecified mitochondrial disorder	21	1.08	0.672	1.59					

PALF: pediatric acute liver failure.
*Etiologies of PALF in developed countries that accounted for less than 1% of diagnoses include: Hepatitis A, Myelodysplastic syndrome, Mushroom toxicity, Mitochondrial respiratory deficiency, Ornithine transcarboxylase deficiency, Respiratory failure, Hypoxia, Fetal distress, Enterovirus, Autoimmune hepatitis type 1 & 2, Leukemia, Tyrosinemia type I, Hematologic/oncologic cause, Hepatitis E, Solid tumor, Gastrointestinal anomaly, Adenovirus, Veno-occlusive disease, Congenital diaphragmatic hernia, Hepatitis B, Parvovirus B19, Influenza, Defect in glycosylation, Niemann pick C, Human herpes virus 6, Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome, Isoniazid toxicity, Lamotrigine toxicity, Gestational alloimmune disease, Chemotherapy, Hodgkins lymphoma, Recurrent acute liver failure.
†Etiologies of PALF in developing countries that accounted for less than 1% of diagnoses include: Non A-G Hep, Cytomegalovirus, Epstein-barr virus, Tyrosinemia 1, Ischemia/hypoxia hemochromatosis, Autoimmune hepatitis type 1 & 2, Sepsis, Fatty acid oxidation defect, Hepatitis E, Herpes simplex virus, Fructose intolerance, Carnitine palmitoyltransferase 1 deficiency, Isoniazid toxicity, Phosphorous ingestion, Mitochondrial disorder, Hepatitis A virus+Hepatitis E virus coinfection, Varicella zoster virus, Urea cycle defect, Reyes syndrome, Firework toxicity, Lymphoma, Cardiomyopathy, Congenital hypopituitarism.

95% CredI 26.3–31.7), followed by unspecified infection (9.52%; 95% CredI 7.86–11.3) and Wilson's disease (7.78%; 95% CredI 6.27–9.44). 20.1% (95% CredI 17.8–22.6) of cases were of indeterminate origin.

Table 4 provides a detailed view of the etiologies of PALF in children in developing countries. Studies that were included in **Table 4** clearly distinguished both the age of the child and diagnosis; all other studies from developing countries were excluded. This resulted in a total of 61 children under the age of 1 year and 562 children over the age of 1 year. Of the 61 children under 1 year of age, the most common etiology was unspecified infection (39.3%; 95% CredI 27.6–51.8), followed by cytomegalovirus infection (13.1%; 95% CredI 5.94–22.6), and metabolic disorder (4.92%; 95% CredI 1.04–11.5). Of the 562 children over 1 year old, the most common etiology was Hepatitis A (32.4%; 95% CredI 28.6–36.3), followed by unspecified infection (14.9%; 95% CredI 12.1–18.0), and autoimmune disorders (3.56%; 95% CredI 2.19–5.24). 18% (95% CredI 14.9–21.2) of cases were of indeterminate origin.

Table 5 provides a detailed view of the etiologies of PALF in children in developed countries. Studies that were included in **Table 5** clearly distinguished both the age of the child and diagnosis; all other studies from developed countries were excluded. This resulted in a total of 93 children under the age of 1 year and 281 children over the age of 1 year. Of the 93 children under 1 year of age, the most common etiology was a metabolic disorder (17.2%; 95% CredI 10.3–25.5), followed by ischemia (14%; 95% CredI 7.74–21.7) and hemochromatosis (12.9%; 95% CredI 6.93–20.4). 15.1% (95% CredI 8.58–23.0) of cases

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Table 4. Etiology of palf in developing countries

Etiology	<1-year-old (n=61)	Mean	95% credible interval		Etiology*	1–21 years old (n=562)	Mean	95% credible interval	
			Lower	Upper				Lower	Upper
Unspecified infection	24	39.3	27.6	51.8	Hepatiti A	182	32.4	28.6	36.3
Cytomegalovirus	8	13.1	5.94	22.6	Indeterminate	101	18	14.9	21.2
Metabolic disorder	3	4.92	1.04	11.5	Unspecified infection	84	14.9	12.1	18
Hemochromatosis	2	3.28	0.406	8.94	Autoimmune disorder	20	3.56	2.19	5.24
Galactosemia	2	3.28	0.406	8.94	Unspecified toxin	19	3.38	2.05	5.02
Congenital hypopituitarism	2	3.28	0.406	8.94	Acetaminophen toxicity	18	3.2	1.91	4.81
Herpes simplex virus	1	1.64	0.0422	5.96	Mushroom toxicity	14	2.49	1.37	3.93
Klebsiella	1	1.64	0.0422	5.96	Albendazole toxicity	11	1.96	0.983	3.25
Hemophagocytic lymphohistocytosis	1	1.64	0.0422	5.96	Non-A-G hepatitis	9	1.6	0.736	2.79
Fructose intolerance	1	1.64	0.0422	5.96	Epstein barr virus	7	1.25	0.503	2.31
Pyruvate carboxylase deficiency	1	1.64	0.0422	5.96	Hemophagocytic lymphohistiocytosis	6	1.07	0.393	2.07

PALF: pediatric acute liver failure.
*Etiologies of PALF in children >1 year old that accounted for less than 1% of the diagnoses include: Hepatitis B, Galactosemia, Fatty acid oxidation defect, Carnitine palmitoyltransferase i deficiency, Isoniazid toxicity, Hepatitis C, Herpes simplex virus, Phosphorous ingestion, Firework ingestion, Ischemia/hypoxia, Cardiomyopathy, Hepatitis E, Hepatitis A+Hepatitis B co-infection, Non-ABC hepatitis, Adenovirus, Dengue virus, Salmonella, Wilson's disease+Hepatitis A, Wilson's disease+Hepatitis E, Hemochromatosis, Niemann pick disease, Wolman's syndrome, Alpers syndrome, Unspecified metabolic disorder, Valproate toxicity, Reye's syndrome, Fluconazole toxicity, Indomethacin toxicity, Isoflurane+Leflunomide toxicity, Meropenem+Isoniazid+Rifampin+Pyrazinamide toxicity, Diphenylhydantoin/phenytoin toxicity, and Non-hodgkin lymphoma.

Table 5. Etiology of palf in developed countries

Etiology	<1-year-old (n=93)	Mean	95% credible interval		Etiology*	1–22 years old (n=281)	Mean	95% credible interval	
			Lower	Upper				Lower	Upper
Metabolic disorder	16	17.2	10.3	25.5	Indeterminate	80	28.5	23.4	33.9
Indeterminate	14	15.1	8.58	23.0	Non-A-B-C hepatitis	23	8.19	5.28	11.7
Ischemia	13	14	7.74	21.7	Acetaminophen toxicity	22	7.83	4.99	11.2
Hemochromatosis	12	12	6.93	20.4	Autoimmune disorder	21	7.47	4.7	10.8
Herpes simplex virus	9	9.68	4.57	16.4	Wilson's disease	18	6.41	3.85	9.54
Hypoxia	8	8.6	3.83	15.1	Unspecified toxin	18	6.41	3.85	9.54
Hepatitis E	5	5.38	1.79	10.8	Metabolic disorder	17	6.05	3.58	9.11
Enterovirus	4	4.3	1.2	9.23	Hepatitis A	13	4.63	2.49	7.37
Hemophagocytic lymphohistiocytosis	3	3.23	0.678	7.63	Hemophagocytic lymphohistiocytosis	8	2.85	1.24	5.08
Cytomegalovirus	2	2.15	0.264	5.91	Mushroom toxicity	8	2.85	1.24	5.08
Galactosemia	2	2.15	0.264	5.91	Autoimmune hepatitis type 1	7	2.49	1.01	4.61
Mitochondrial respiratory deficiency	2	2.15	0.264	5.91	Autoimmune hepatitis type 2	7	2.49	1.101	4.61
Myelodysplastic syndrome	2	2.15	0.264	5.91	Hepatitis B	3	1.07	0.222	2.56
Gestational alloimmune liver disease	1	1.08	3.93	0.028	Parvovirus B19	3	1.07	0.222	2.56
					Influenza	3	1.07	0.222	2.56
					Veno-occlusive disease	3	1.07	0.222	2.56

PALF: pediatric acute liver failure.
Etiologies of PALF in children >1-year-old that accounted for less than 1% of the diagnoses include: Unspecified infection, Ornithine transcarbamylase deficiency, Hyperornithinemia- hyperammonemia-homocitrullinemia syndrome, Isoniazid toxicity, Mitochondrial disorder, Hodgkins lymphoma, Herpes simplex virus, Human herpes virus-6, Epstein-barr virus, Echovirus, Parainfluenza, Hemochromatosis, Galactosemia, Glycogen storage disease, Fatty acid oxidation disorder, Valproate toxicity, Lamotrigine toxicity, Carbamazepine toxicity, Non-steroidal inflammatory drug toxicity, Mitochondrial respiratory deficiency, Reye's syndrome.

were of indeterminate origin. Of the 281 children over 1 year old, the most common etiology was Non-A-B-C hepatitis (8.19%; 95% CredI 5.28–11.7), followed by acetaminophen toxicity (7.83%; 95% CredI 4.99–11.2) and autoimmune disorders (7.47%; 95% CredI 4.7–10.8). 28.5% (95% CredI 23.4–33.9) of cases were of indeterminate origin.

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DISCUSSION

Comprehensive review of PALF literature between 1997-2019 yielded 32 full text articles for a sum of 2,989 children that were included in this systematic review. These children originated from both developed and developing countries and spanned the age range of 0–22 years old. Results demonstrate that developmental status of the country and age of the child are important determinants of the etiologies of PALF.

The top three diagnoses of PALF in developing countries were: Hepatitis A infection (28.9%; 95% CredI 26.3–31.7), unspecified infection (9.52%; 95% CredI, 7.86–11.3), and Wilson's disease (7.78%; 95% CredI 6.27–9.44), whereas in developed countries the top three most common diagnoses were acetaminophen toxicity (9.24%; 95% CredI 7.99–10.6), unspecified metabolic disorder (5.47%; 95% CredI 4.5–6.52), and unspecified infections (5.06%; 95% CredI 4.13–6.08). Children under 1 year old in developed countries were most commonly diagnosed with an unspecified metabolic disorder (17.2%; 95% CredI 10.3–25.5), whereas children under 1 year old in developing countries were most commonly diagnosed with an unspecified infectious etiology (39.3%; 95% CredI 27.6–51.8). Children greater than 1 year old in developed countries with PALF were most commonly diagnosed with non-A-B-C hepatitis (8.19%; 95% CredI 5.28–11.7) whereas in developing countries Hepatitis A infection (32.4%; 95% CredI 28.6–36.3) was the most common diagnosis.

Clearly, the frequencies in etiologies of PALF differ between developed and developing countries, and as such it is an important factor to consider in the diagnosis of PALF. In both developed and developing countries, stratification of the data by age range also yields different frequencies of the etiologies of PALF. While some of the discrepancy in frequencies according to age group may be attributed to exclusion of articles that did not specify the ages of their children, it also highlights the importance of taking a child's age into account when approaching a patient with PALF.

The etiologies of PALF and their relative frequencies listed in the present review differ from previous analyses. In a review by Squires et al. [46,47], acetaminophen toxicity was found to be the most common etiology of PALF in all children 0–18 years. The cohort of children in this analysis originated solely from developed countries and was substantially smaller than the population of children in the present study. In another review of PALF, Dhawan lists metabolic etiologies as the most common cause of PALF in North America and Europe, and Hepatitis A as the most common etiology in Asia and South America [48]. Neither of these studies were systematic reviews. The study presented here categorized data by developed and developing countries and found Hepatitis A to be the leading cause of PALF in developing countries, while acetaminophen toxicity was the leading cause in developed countries.

Limitations

As a systematic review, this article has inherent limitations. The etiologies of PALF listed in the articles utilized for this study were taken at face value (as reported by their respective studies), resulting in vague etiologies such as non-A-B-C Hepatitis and unspecified infection. Available diagnostic resources, criteria, and rigor of evaluation were not standardized across institutions, accounting, in part, for the large number of indeterminate or unspecified etiologies of PALF and raising issues about diagnostic consistency. Age categories were established with the goal of including as many patients as possible in each category. While efforts were made to contact authors regarding age distributions, many studies did not include this information and were excluded from age analysis, resulting in a smaller sample

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size in **Tables 4** and **5** compared to **Tables 3** and **4**. Unfortunately, most of the studies that did provide age ranges reported those ranges as 0–1 year old and >1 year old. As such, the age category of 1–22 years was unable to be narrowed because specific ages for children in that category were mostly unavailable. One other consequence of this issue was the fact that 90% of children aged 0-1 in developed countries were 0 to 28 days of age. This highlights the need for future studies to report the ages of their patients more specifically, so that the differential diagnosis for PALF can be narrowed according to the child's age category.

Conclusion

In summary, the leading causes of PALF in children aged 0–22 years in developed and developing countries were different. Moreover, sub-analysis of these children by age yielded distinct etiologies, suggesting that both the age of the child and socioeconomic status of the child's country of origin need to be considered in the evaluation of children with PALF. Future studies need to be prospective and geographically diverse; clinical evaluations need to be complete and consistent, while diagnostic criteria need to be strict and well-defined.

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