



Original Research

Frequency and Prognosis of Hydrops Fetalis: A 10-Year Single-Center Experience

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Abstract

Objective: The study aims to evaluate the etiological distribution and prognosis of newborn infants with hydrops fetalis (HF).

Methods: All infants born in our hospital within the past 10 years and hospitalized with the diagnosis of HF were included in this retrospective descriptive study. Demographic characteristics, etiological distributions, treatment interventions, and prognosis information of the infants were recorded retrospectively. Infants with incomplete data were excluded from the study.

Results: The mean gestational age of infants with HF was 33.6 ± 3.1 weeks, and the mean birth weight was 2444 ± 792 grams. Of the HF cases, 90.5% were born by cesarean section and the prenatal diagnosis rate was 42.9%. About 57.1% of the infants were intubated during resuscitation at birth in the delivery room. In the NICU, 81% of the cases were intubated and 71.4% received surfactant treatment. The most common HF findings were ascites (81%) and subcutaneous edema (81%). The most common interventional procedures were paracentesis (81%) and thoracentesis (52.4%). Exchange transfusion was performed in 2 cases (9.5%) due to immune HF. The mortality rate in the study group was 52.4%. Considering the etiological distribution of HF cases in the study group, three cases were diagnosed with immune HF (14.3%) and 18 cases with non-immune hydrops fetalis (NIHF) (85.7%). The underlying cause in immune HF cases was rhesus incompatibility. In cases with NIHF, idiopathic (23.8%) and cardiovascular diseases were the most common etiologies. A significant relationship was found between delivery room management and mortality. While the need for intubation in delivery room was significantly higher in non-survivors, the frequency of applying only positive pressure ventilation in the delivery room was significantly higher in survivors. While the rate of survival was 66.7% in immune HF cases, it was 44.4% in NIHF cases.

Conclusion: The risk of perinatal mortality in infants with HF is high depending on the underlying cause. In this study, it was determined that HF mostly developed for non-immune reasons, prenatal diagnosis and follow-up were insufficient and the interventions performed in the delivery room were an important factor in predicting mortality in the follow-up of neonates with HF.

Keywords: Edema, Hydrops fetalis; mortality; newborn; prognosis.

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Introduction

Hydrops fetalis (HF) is defined as abnormal fluid accumulation in at least two different fetal body cavities (peritoneum, pericardium, pleura, and skin).^[1] Polyhydramnios and increased placental thickness are often associated accompanying findings.^[2] The frequency of HF has been reported as 1/1700–1/3000 in pregnancies in other studies.^[1,3] HF is defined as immune when it develops due to rhesus (Rh) incompatibility and as non-immune hydrops fetalis (NIHF) when it develops due to other reasons.^[4] With the widespread use of anti-D immunoglobulin (Rhogam) prophylaxis, the frequency of Rh incompatibility has decreased, as a result, NIHF now accounts for estimated 76–87% of cases of hydrops.^[5]

The underlying pathogenesis in NIHF cases is complex. Impairment of fetal fluid flow between interstitial and vascular areas of the fetus because of increased central venous pressure, low plasma oncotic pressure, or decreased lymphatic flow can be seen as the causes of the pathogenesis.^[6] Many different causes such as cardiovascular diseases, chromosomal disorders, hematological anomalies, inborn errors of metabolism, congenital infections, gastrointestinal and renal diseases, intrathoracic masses and lymphatic vessel dysplasia, twin-to-twin transfusion, placental causes, and genetic syndromes may play a role in the etiology of the disease.^[5] While chromosomal anomalies are the most common etiology in HF cases detected in early gestational weeks, cardiovascular anomalies are most common in late gestational weeks.^[5,7-12]

Despite the advances in neonatal intensive care practices and improvements in perinatal ultrasonography, molecular and genetic fields, the mortality, and morbidity rates in HF cases continue to be high. In studies conducted, it has been reported that the mortality rate in the neonatal period in NIHF cases is between 32% and 98%.^[4,8-11,13-16] It is known that many problems, especially neurological problems, are seen in surviving infants.^[11]

In this study, it was aimed to determine the etiological causes, mortality rates, and the effects of prognostic factors on mortality in infants with the HF in our clinic in the past 10 years.

Methods

All infants born with a diagnosis of HF between January 1, 2012, and January 1, 2021 (over 10 years) in Sisli Hamidiye Etfal Training and Research Hospital neonatal intensive care unit (NICU) were included in this single-center, descriptive retrospective study. The NICU of our hospital serves as an advanced center with a total of 28 beds, 20 of which are at

the third level and 8 at the second level. Our hospital is tertiary perinatal center with 3500–4000 births and approximately 850–900 new born admitted per year.

Study Design

During the study period, infants hospitalized in the NICU were scanned electronically using the ICD codes P56.9, P83.2, P56.0, and P56 from the hospital information system. The files of the infants included in the study were accessed electronically and the data obtained were recorded in the created study form.

The diagnosis of HF was made when abnormal fluid accumulation was detected in at least two of the peritoneum, pleura, pericardium, and skin (skin thickness >5 mm). Patients who were born in external center and were referred to our clinic, stillborn, and patients with missing patient data were excluded from the study. Approval for the study was obtained from the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital (Date: 08/06/2021, Decision number: 1912).

Prenatal history, maternal age, consanguineous marriage, birth type, gestational age, gender, birth weight, whether the infant was diagnosed prenatally, and presence of congenital anomaly were recorded in the study form from the files of the infants included in the study.

Laboratory analysis to determine the cause of HF; complete blood count, biochemistry, peripheral smear, coombs test, blood groups, hemoglobin electrophoresis, glucose 6-phosphate dehydrogenase enzyme level, metabolic disease screening tests (tandem mass spectrophotometer, urine and blood amino acids, urine organic acid level, and ammonia), and serological test results for intrauterine infections such as toxoplasma, cytomegalovirus, herpes simplex, rubella, parvovirus B19, syphilis, and the karyotype analysis results were recorded. Ultrasonographic examinations, echocardiography, computed tomography, and magnetic resonance imaging results, which are imaging methods for etiology, were examined and recorded in the study form.

Presence of ascites, pericardial effusion, pleural effusion, and interventional procedures performed in the delivery room and during the NICU admissions for HF cases, delivery room management (intubation, positive pressure ventilation, or cardiac compression), intubation frequency and surfactant requirement, etiological causes, and prognostic status data were recorded. The infants included in the study were compared in terms of demographic characteristics, interventions, and treatments as the survivors and the non-survivors. The risk factors for predicting mortality were analyzed. Interventions for babies in the delivery

room were grouped as only positive pressure ventilation, positive pressure ventilation + intubation, and positive pressure ventilation + intubation + cardiac compression, and their effects on mortality were compared.

Statistical Analysis

The SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The conformity of univariate data to normal distribution was evaluated with the Shapiro–Wilk Francia test, while homogeneity of variance was evaluated with the Levene test. The independent samples *t*-test was used with Bootstrap results, while the Mann–Whitney U-test was used with Monte Carlo results in the comparison of two independent groups according to quantitative data. In the comparison of categorical variables, the Fisher exact and Fisher-Freeman-Holton tests were tested with the Monte Carlo Simulation technique, and the column ratios were compared with each other and expressed according to the Benjamini-Hochberg corrected *p* value results. While quantitative variables were expressed as mean (standard deviation) and median (minimum/maximum) in the tables, categorical variables were shown as *n* (%). Variables were analyzed at 95% confidence level and the *P* value was considered significant when it was <0.05.

RESULTS

During the study period, 23 patients were hospitalized with the diagnosis of HF. Two patients whose file data could not be fully accessed were excluded from the study. Demographic and clinical characteristics of 21 cases included in the study are given in Table 1. The mean gestational age of the cases included in the study was 33.6±3.1 weeks and the mean birth weight was 2444±792 g. About 90.5% (*n* = 19) of the cases included in the study were born by cesarean section. While the rate of consanguineous marriage was 47.6% in the study group, it was found that 42.9% of the cases were diagnosed with HF in the prenatal period. About 57.1% (*n*=12) of the cases were intubated and cardiac compression was applied to 9.5% of the study group. During their hospitalization in the NICU, 81% of the cases were treated with intubation, 71.4% were treated with intratracheal surfactant, and pneumothorax developed in 23.8% of the cases. The most common findings of HF in the cases were ascites (81%) and subcutaneous edema (81%). Paracentesis was performed in 81% of the cases in the NICU follow-up, and it was the most frequently performed interventional procedure. Thoracentesis was applied to the cases in the second frequency, and a thorax tube was inserted in 42.9% of the cases due to pneumothorax or pleural effusion. Exchange transfusion was performed in two patients with

a diagnosis of severe immune HF with severe hemolysis and elevated indirect bilirubin. The mortality rate in the study group was 52.4%.

The distribution of etiological causes detected in the cases included in the study is given in Table 2. Of the patients, 14.3% were diagnosed with immune HF and 85.7% with NIHF. Immune HF cases were due to Rh incompatibility. Considering the etiology of the NIHF cases, cardiovascular causes were determined in 4 cases (19,04%), twin-to-twin transfusion syndrome in 2 cases (9.5%), congenital metabolic disease in 2 cases (9.5%), chromosomal/syndromic causes in 3 cases (14.3%), and chromosomal/syndromic causes in 1 case, pulmonary hypoplasia in 1 case (4.8%), and skeletal dysplasia in 1 case (4.8%). The idiopathic group included 5 cases (23.8%) without any underlying cause in the etiology of NIFH.

Survivors and non-survivors were compared in terms of demographic and clinical characteristics (Table 3). There

Table 1. General characteristics of the newborns with hydrops fetalis included in the study

Characteristics	<i>n</i> (%)
Gestational week (week) (Mean±SD*)	33.6±3.1
Birth weight (gram) (Mean±SD*)	2444±792
Normal spontaneous delivery/cesarean section	2 (9.5)/19 (90.5)
Female/male	11 (52.4)/10 (47.6)
Multiple pregnancy	5 (23.8)
Consanguineous marriage	10 (47.6)
Prenatal diagnosis	9 (42.9)
Delivery room management	
Intubation	12 (57.1)
Positive pressure ventilation	7 (33.3)
Cardiac compression	2 (9.5)
Need for surfactant treatment	15 (71.4)
Pneumothorax	5 (23.8)
Skin edema (>5 mm)	17 (81)
Pleural effusion	9 (42.9)
Ascites	17 (81)
Applied interventional procedures	
Thoracentesis	11 (52.4)
Paracentesis	17 (81)
Blood exchange	2 (9.5)
Thoracic tube placement	9 (42.9)
Mortality rate	11 (52.4)

SD: Standard deviation.

Table 2. Etiological distribution of the infants included in the study (n=21)

Etiology	n (%)
Immune hydrops fetalis	3 (14.3)
Non-immune hydrops fetalis	18 (85.7)
Causes of non-immune hydrops fetalis	
Cardiovascular disease	4 (19.04)
Pulmonary stenosis	1 (4.8)
Aortic hypoplasia	1(4.8)
Complete atrioventricular block	1(4.8)
Hypoplastic left heart syndrome	1(4.8)
Twin-to-twin transfusion	2 (9.5)
Inborn errors of metabolism	2 (9.5)
Chromosomal/syndromic	3 (14.3)
Cerebellar hypoplasia	1 (4.8)
Congenital hypotonia	1 (4.8)
Genetic syndrome	1 (4.8)
Pulmonary hypoplasia	1 (4.8)
Skeletal dysplasia (Arthrogryposis multiplex)	1 (4.8)
Idiopathic	5 (23.8)

was no difference between survivors and non-survivors in terms of birth weight, gestational age, mode of delivery, gender, and prenatal diagnosis. However, it was determined that there was a significant relationship between delivery room practices and mortality ($P = 0.023$). It was found that the need of intubation was significantly higher (81.8%) in non-survivors group and the need of only positive pressure ventilation was high (60%) in survivors group (P value; 0.017 and 0.013, respectively) (Figure 1). There was no difference in the frequency of surfactant administration, clinical findings of HF, and interventional procedures in survivors and non-survivors. When the survival of HF cases in the study group was evaluated, survival in immune HF was 66.7% and in NIHF cases was 44.4%. The prognosis of the cases in the idiopathic group resulted in 80% survival. All NIHF cases due to cardiovascular disease had died.

Discussion

Despite the advances in prenatal follow-up and neonatal intensive care practices, HF continues to be an important

Table 3. Comparison of demographic and clinical characteristics of infants in survivors and non-survivors

Characteristics	Total (n=21)	Survivors (n=10)	Non-survivors (n=11)	P
Birth weight (gram), median	2730	2790	2490	0.671 ^u
Gestational age (week), mean (SD.)	33.6 (3.17)	34.1 (2.42)	33.2 (3.80)	0.574 ^t
Gender (male), n (%)	10 (47.6)	5 (50.0)	5 (45.5)	0.999 ^f
Mode of delivery (cesarean section), n (%)	2 (9.5)	0 (0.0)	2 (18.2)	0.476 ^f
Prenatal diagnosis, n (%)	9 (42.9)	4 (40.0)	5 (45.5)	0.999 ^f
				0.023 ^{ff}
Delivery room management, n (%)				
Intubation	12 (57.1)	3 (30.0)	9 (81.8) ^A	0.017 ^b
Positive pressure ventilation	7 (33.3)	6 (60.0) ^B	1 (9.1)	0.013 ^b
Cardiac compression	2 (9.5)	1 (10.0)	1 (9.1)	Ns.
Need for surfactant treatment, n (%)	15 (71.4)	7 (70.0)	8 (72.7)	0.999 ^f
Skin edema, n (%)	17 (81.0)	8 (80.0)	9 (81.8)	0.999 ^f
Pleural effusion, n (%)	9 (42.9)	5 (50.0)	4 (36.4)	0.670 ^f
Pericardial effusion, n (%)	1 (4.8)	0 (0.0)	1 (9.1)	0.999 ^f
Ascites, n (%)	17 (81.0)	7 (70.0)	10 (90.9)	0.311 ^f
Applied interventional procedures, n(%)				
Thoracentesis	11 (52.4)	5 (50.0)	6 (54.5)	0.999 ^f
Paracentesis	17 (81.0)	7 (70.0)	10 (90.9)	0.311 ^f
Pericardiocentesis	0 (0.0)	0 (0.0)	0 (0.0)	-
Blood exchange	2 (9.5)	2 (20.0)	0 (0.0)	0.214 ^f
Thoracic tube placement	9 (42.9)	6 (60.0)	3 (27.3)	0.198 ^f

^uIndependent samples t-test (bootstrap), ^tMann–Whitney U-test (Monte Carlo), ^fFisher’s exact Test (Monte Carlo); ^{ff}Fisher’s-Freeman-Halton test (Monte Carlo); *post hoc* test: ^BBenjamini-Hochberg test, SD: Standard deviation, ^Aexpresses significance according to the surviving group, ^Bexpresses significance according to the non-survivors group, Ns.: Not significant.

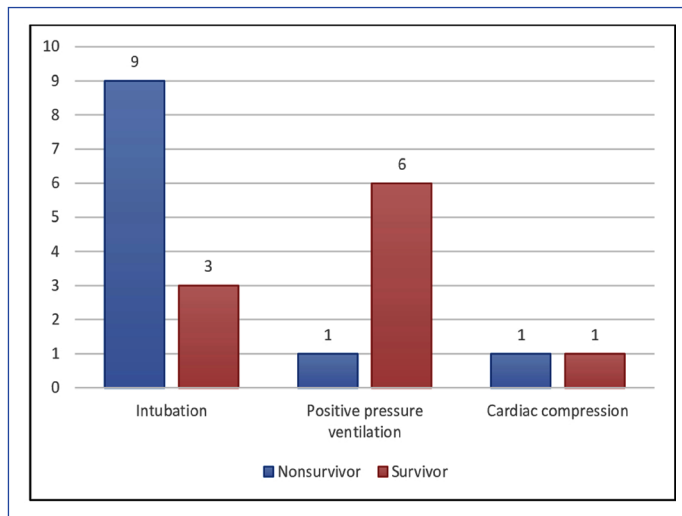


Figure 1. Delivery room management in survivors and non-survivors.

cause of mortality and morbidity. In the current study, it was determined that the majority of HF cases had NIHF, 52.4% of the cases diagnosed with HF died, 42.9% had prenatal follow-up and was diagnosed with antenatal HF, the most common clinical findings were ascites and subcutaneous edema, and the frequency of intubation in delivery room was higher in non-survivors.

While immune causes decrease in HF cases with anti-D immunoglobulin (Rhogam) administration, they are more common in NIHF etiology. In developing countries, 38.3% of all HF cases have been reported as immune HF.^[15] In studies reported from our country in recent years, it has been reported that 32.6–45.2% of HF cases are immune HF.^[4,8-9] The high rate of immune HF detected in these studies is attributed to the fact that these centers are the tertiary perinatal center for high-risk pregnant women and that pregnant women with Rh immunization are referred from external centers in late gestational weeks. In the current study, 85.7% of HF cases were found to be NIHF.

When NIHF cases, which constitute the majority of HF cases, are evaluated in terms of underlying etiology, it is reported that chromosomal anomalies are observed in early gestational weeks, while cardiac structural anomalies often play a role in the etiology after 22 weeks of gestation.^[5,7-12] However, in a recent study, the most common etiology of NIHF cases was 28.4% hematological diseases and 19.8% chromosomal anomalies.^[17] The high rates of hematological diseases and chromosomal anomalies in etiology were attributed to regional differences, the inclusion of first trimester pregnancies in the study, and the high frequency of NIHF detected in this region. Takci *et al.*, 12.9% lymphatic dysplasia was found to be

the second most common etiological cause after the idiopathic group in NIHF cases, and mortality was reported to be quite low in this group.^[4] In the study in which the etiology of 1338 cases diagnosed with NIHF was evaluated, cardiovascular causes were found to be the most common etiological cause with a rate of 20.1%.^[18] In the current study, after the idiopathic group, cardiovascular causes were the most common etiology. In the study by Karadag *et al.*, it was reported that 32% of NIHF cases had cardiovascular diseases in the etiology.^[9]

In NIHF cases, the frequency of metabolic disease is reported to be 1–2%.^[5,18] Moreno *et al.* found congenital metabolic disease in 6% of 53 cases when they used an expanded screening program for inborn errors of metabolic disease.^[19] In the current study, metabolic disease was detected in 9.5% of HF cases. The rate of metabolic disease in the etiology we found is similar to the rate of 9% reported in the study.^[4] It is considered that the high frequency of inborn errors of metabolism in the etiology of HF in our country is due to the high rate of consanguineous marriage.

In studies in the literature, the incidence of idiopathic group in NIHF cases has been reported to be between 14% and 35.9%.^[4,7,12,17,20,21] Recently, in a study evaluating NIHF cases, it was reported that 72% of the cases were diagnosed and no etiology could be found in 28%.^[17] However, in a retrospective study in which antenatal invasive tests were performed, the underlying diagnosis was determined in 86% of the cases.^[21] In the current study, the idiopathic group was the most common etiology, which was attributed to reasons such as the lack of perinatal follow-up of these cases, the short time between hospitalization and delivery, and the loss of patients before the necessary tests could be performed.

Clinical and ultrasonographic findings of subcutaneous edema, abdominal ascites, pleural effusion, pericardial effusion, increase in placental thickness, and polyhydramnios are important in diagnosing HF. Kizilelma *et al.*^[20] stated that the most common clinical findings in NIHF cases were subcutaneous edema detected in all patients and neonatal ascites was the second most common with a frequency of 84.6%. In another study, subcutaneous edema was detected in 72% and ascites with a frequency of 44%, while pleural effusion was found in 28% and pericardial effusion in 20%.^[9] Similarly, in the current study, fetal ascites and subcutaneous edema were the most common clinical findings in 80% of the patients.

Newborns with of HF, when the underlying cause is severe erythroblastosis, intrauterine intravascular blood transfusions can be performed through cordocentesis with ultrasound guidance. In the current study, intrauterine

intravascular blood transfusion was not performed in immune HF cases due to Rh incompatibility. This was attributed to the fact that the patients were not followed up and were diagnosed with HF just before delivery.

The widespread use of prenatal ultrasonography today enables HF cases to be diagnosed at an early stage, to be referred to advanced centers where antenatal follow-up will be made, and to deliver delivery in centers with tertiary NICUs. In the current study, approximately half of the HF cases did not have prenatal follow-up. In studies conducted in our country, the rate of prenatal diagnosis is reported as 40–56.5%.^[4,9,20] In our country, the deficiencies and inadequacies in the prenatal follow-up of half of the HF cases cause the chance of antenatal therapeutic treatment in these infants to be given in the tertiary perinatal center and decrease the follow-up of HF cases in the NICU, leading to an increase in mortality and morbidity. In addition, half of the cases in our study group had a history of consanguineous marriage. The high rate of consanguineous marriage in the current study increases the risk of both autosomal recessive genetic/syndromic diseases and inborn errors of metabolism. Reducing consanguineous marriages will also reduce the incidence of NIHF by reducing the risk of developing an autosomal recessive genetic disease.

In the current study, there was no difference in terms of birth weight, gestational age, and clinical findings when survivors and non-survivors were compared. However, a significant correlation was found between delivery room interventions and mortality. The need for intubation in delivery room was significantly higher in non-survivors. In addition, the frequency of positive pressure ventilation in the delivery room was significantly higher in survivors. In a study comparing the survivor and non-survivor NIHF cases, it was reported that while the gestational age and birth weight were significantly lower in the non-survivors, the need for resuscitation at birth, surfactant treatment, and fluid accumulation in two or more cavities was found to be significantly higher.^[4] However, it was reported that gestational age had a low predictive value (ROC AUC 0.61 and 0.60, respectively) in predicting neonatal mortality and mortality at discharge, and the presence of ascites was a significant risk factor independent of the gestational week.^[7] Recently reported that the rate of need for resuscitation at birth, need for mechanical ventilation, presence of ascites and pleural effusion was high, and birth weight was lower in non-survivors cases with HF.^[8]

HF is an important cause of mortality and morbidity.^[4,7-8,10,13-15,17] It has been reported that mortality in NIHF cases in the neonatal period is between 32% and

98%, and mortality in NIHF cases is higher than in immune HF cases.^[4,7-17,20,22-24] In a recently published study involving HF infants including termination, spontaneous abortion, and intrauterine fetal losses, the survival rate in the neonatal period was found to be very low as 19.7%.^[17] Differences in mortality rates in HF cases have been reported to vary depending on the gestational week, whether termination cases were included in the study, and whether the infants were born alive or not.^[12,25,26] Similar to the results of previously reported studies, 52.4% of HF cases in this study died before discharge. In the current study, the mortality rate was found to be 33.3% in immune HF, while this rate was 55.6% in NIHF cases.

It has been reported that the underlying etiology, birth weight, and APGAR score at the 1st and 5th min of gestation, intubation, and chest compression in the delivery room, low serum albumin concentration, need for thoracentesis, and fluid accumulation in more than 2 body cavities are significant prognostic factors in predicting prognosis in neonatal HF.^[4,8,10-11,16,17,22,25-27] The prognosis also depends on the age of onset of hydropic changes and is associated with worse outcomes in cases of early-onset HF.^[16] It is known that diagnosis in late gestational weeks and prognosis in delivery in late gestational weeks are better.^[10,13,14,23,26,28-30] It is known that some of the HF cases regress antenatally and the prognosis is better in these cases.^[12,19,31]

The underlying etiology also affects survival in HF cases. The prognosis is poor in aneuploidy, structural cardiovascular anomalies, non-cardiac structural thoracic anomalies, and placental anomalies.^[13,28] It has been found that the prognosis is better in cases where chylothorax, chylous ascites, gastrointestinal causes, infections (especially Parvovirus), and arrhythmia cause NIHF.^[4,10,28] It has been reported that the mortality rate in lymphatic dysplasia is very low at 12.5%.^[4] In one study, survival rates were as high as 71.4% in gastrointestinal causes, 52.7% in the idiopathic group, and 42.2% in lymphatic defects, while it was found at very low rates (0.2–1.1%) in syndromic, chromosomal, and hematological diseases.^[17] Cystic hygroma is the most common cause of fetal loss before 22 weeks of gestation and is often associated with major structural anomalies and chromosomal disorders.^[10] In a study evaluating the prognosis in NIHF cases according to the underlying etiology, it was reported that cardiovascular diseases cause both intrauterine fetal losses and death in the 1st year of life, and complications develop after 1 year of age in survivors.^[11] In the current study, 80% of the patients in the idiopathic group survived, while all HF patients with cardiovascular disease died.

The study has some limitations. Due to the small number of cases, the contribution of especially etiological subgroups to the prognosis could not be evaluated strongly. The retrospective nature of the study is another limitation of it. Since antenatal follow-ups were not available in our hospital, clear information about the onset of HF could not be obtained. Since only live-born infants were included in the study, cases with spontaneous resolution, intrauterine abortions, and intrauterine fetal losses are unknown during the study period. Finally, another limitation of the study is the inability to evaluate the 1st year mortality and neuro developmental prognosis due to the lack of long-term follow-up of surviving infants after discharge.

Conclusion

Today, HF is still a disease with high mortality and morbidity and the mortality rate was found 52.4% in our study. The frequency of intubation in the delivery room was significantly higher in non-survivors. We found that 85.7% of HF cases were NIHF and 14.3% were immune HF cases, consanguineous marriage rate was 47.6%, prenatal diagnosis rate was 42.9%, the most common symptoms were subcutaneous edema (81%) and abdominal ascites (81%) and the most common etiology in NIHF cases were idiopathic and cardiovascular causes. It is considered that regular antenatal follow-up, referral of pregnant women with HF to tertiary perinatology centers and follow-up in these centers, and delivery in experienced tertiary NICUs can reduce mortality and morbidity.

Disclosures

Ethics Committee Approval: This Study was approved by Sisli Hamidiye Etfal Training and Research Hospital Local Ethics Committee (Date:08/06/2021, number: 1912).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.T.U., A.B.; Design – A.B., E.T.U.; Supervision – A.B., H.S.U.; Materials – E.T.U., A.B., E.K.B.; Data collection &/or processing – E.T.U.; Analysis and/or interpretation – E.T.U., A.B.; Literature search – E.T.U., E.K.B.; Writing – E.T.U.; Critical review – A.B., H.S.U.

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