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# Pediatric malignant hyperthermia: risk factors, morbidity, and mortality identified from the Nationwide Inpatient Sample and Kids' Inpatient Database

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## Summary

**Background:** Malignant Hyperthermia (MH) is a potentially fatal metabolic disorder. Due to its rarity, limited evidence exists about risk factors, morbidity, and mortality especially in children.
**Methods:** Using the Nationwide Inpatient Sample and the Kid's Inpatient Database (KID), admissions with the ICD-9 code for MH (995.86) were extracted for patients 0–17 years of age. Demographic characteristics were analyzed. Logistic regression was performed to identify patient and hospital characteristics associated with mortality. A subset of patients with a surgical ICD-9 code in the KID was studied to calculate the prevalence of MH in the dataset.
**Results:** A total of 310 pediatric admissions were seen in 13 nonoverlapping years of data. Patients had a mortality of 2.9%. Male sex was predominant (64.8%), and 40.5% of the admissions were treated at centers not identified as children's hospitals. The most common associated diagnosis was rhabdomyolysis, which was present in 26 cases. Regression with the outcome of mortality did not yield significant differences between demographic factors, age, sex race, or hospital type, pediatric vs nonpediatric. Within a surgical subset of 530 449 admissions, MH was coded in 55, giving a rate of 1.04 cases per 10 000 cases.
**Conclusions:** This study is the first to combine two large databases to study MH in the pediatric population. The analysis provides an insight into the risk factors, comorbidities, mortality, and prevalence of MH in the United States population. Until more methodologically rigorous, large-scale studies are done, the use of databases will continue to be the optimal method to study rare diseases.

## Introduction

Malignant hyperthermia (MH) is a rare, inherited metabolic disorder provoked by exposure to halogenated volatile anesthetic gases and succinylcholine. Genetic predisposition is mainly due to a mutation of the RYR1 gene found on chromosome 19q13.1, while a mutation of the CACNA1S gene on chromosome 1q32 accounts for 1% of reported MH cases (1). The RYR1 gene mutation codes for an abnormal ryanodine receptor protein responsible for controlling the release of calcium from the sarcoplasmic reticulum into the myoplasm. The unregulated release of calcium instigates a cascade of physiologic events resulting in metabolic and respiratory acidosis, hyperkalemia, and rhabdomyolysis. The number of causative mutations is unknown, because every new MH case may potentially yield a novel causative mutation. The current number of documented

causative mutations for the RYR1 gene is 31 (2). The number of individuals harboring the gene defect is even more difficult to ascertain based on the variable presentation of the disorder and lack of outward signs and symptoms.

The main barrier to truly understanding the nature of malignant hyperthermia has been the lack of well-controlled clinical trials in humans and dependency on case reports and retrospective studies. Unfortunately, prospective randomized human trials are not feasible due to the fact that it will be unethical to administer a trigger to a MH-susceptible patient. Also, hindering this effort is the genetic predisposition and phenotypic expression of the disorder. There are several hundred mutations of the RYR1 gene, but only 31 documented causal mutations for MH. While some patients experience an early onset and rapid progression of MH resulting in death, others may have multiple anesthetics without incident.

The reduced penetrance and variable expressivity along with the rarity of the disease necessitates the use of databases to develop an understanding of the prevalence, risk factors, and outcomes of patients affected with MH. One study examining 3 years of data from the Kids' Inpatient Database (KID) found 175 MH cases with an overall prevalence of 3.0 per 100 000 hospital discharges (3). Since this study, the KID database has expanded to include the year 2009. In addition, the Nationwide Inpatient Sample (NIS) contains information concerning pediatric hospital discharges from 1988 to 2010 for each year. The reported mortality rate has been found to be 1.4 to 11.2%. However, when studying a different outcome than mortality, a more alarming 35% morbidity rate was found in one study looking at complications associated with MH (4). The current study combines and analyzes two national databases, the KID and NIS datasets, containing discharge information for over 56 million pediatric admissions to achieve a better understanding of the prevalence of MH in the pediatric population and the associated patient profile and mortality in the United States.

## Materials and methods

The Institutional Review Board at our institution approved the present analysis. The study population was obtained from the Hospital's Cost and Utilization Project (HCUP) KID and NIS datasets. The International Classification of Disease 9th version (ICD-9) code for MH (995.86) was introduced in 1998; therefore, nonoverlapping years of NIS and KID were queried from 1998 to 2010. Admissions that had the diagnosis code 995.86 were included for analysis, and the pediatric subset was defined as 0–17 (inclusive) years of age.

Initially, a chi-square test was performed to compare mortality rates in pediatric and adult subgroups. Demographic characteristics such as age (categorized in groups) and sex along with hospital type were studied in the pediatric population.

A Wald's test of uni- and multivariate regression analysis was performed; mortality was used as the outcome and demographic factors as exposures; only admissions from KID were used because NIS did not record the variable for hospital type (children's center or general hospital).

A subset of patients from the study population was selected based on having an ICD-9 procedure code that described a surgical intervention requiring general anesthesia (GA). There is no ICD-9 code for the provision of GA; therefore, to establish this subset of pediatric patients, a list of the most common 500 noncardiac surgical procedures was obtained from the American College of Surgeons National Surgical Quality Improvement Program Pediatric (NSQIP-P) dataset. Based on previous reports, the 500 procedures listed covered >99% of the operations that NSQIP-P captures (5). Two authors (TK and JHS) reviewed the list and concluded that all of these procedures may have required GA. The prevalence of MH in surgical admissions was calculated using this subset. Incidence of MH diagnosis among surgical admissions was calculated using only the KID dataset (years 2000, 2003, 2006, and 2009) of this subset. The NIS utilizes a hospital-based sampling method, and therefore, the incidence calculations could be biased by over- or undersampling of high-risk hospitals.

## Results

During the 13 years of data analyzed, the diagnosis of MH was coded in 1237 adult (≥18 years of age) admissions and 310 pediatric (<18 years of age) admissions. The total mortality for all age groups was 15.1% (234 of 1547), and the rates between age categories were significantly different ($P < 0.001$). (Table 1) Pediatric patients had a mortality of 2.9% and adults 18.2%. A total of 201 pediatric admissions (64.8%) were male, and of the patients with available information on race and hospital type, the majority were white (58.3%) or treated at centers not identified as children's hospitals (40.5%). (Table 2).

The combined database of the NIS and KID was analyzed for previously reported comorbidities associated with MH based on total number of admissions and admissions with MH. (Table 3) The most common relevant associated diagnosis within pediatric admissions was rhabdomyolysis, which was present in 26 cases.

**Table 1** Discharge status among age groups in patients with MH

| Age (years) | Discharge status | | Total |
|---|---|---|---|
| | Alive *n* (%) | Dead *n* (%) | |
| 0–17 | 301 (97.1) | 9 (2.9) | 310 |
| <1 | 32 (100.0) | 0 (0.0) | 32 |
| 1–3 | 86 (97.7) | 2 (2.3) | 88 |
| 4–11 | 84 (97.7) | 2 (2.3) | 86 |
| 12–17 | 99 (95.2) | 5 (4.8) | 104 |
| 18–44 | 512 (86.8) | 78 (13.2) | 590 |
| 45–64 | 333 (79.1) | 88 (20.9) | 421 |
| >65 | 167 (73.9) | 59 (26.1) | 226 |
| Total | 1313 (84.9) | 234 (15.1) | 1547 |

$P < 0.001$ for differences in discharge status among groups.

**Table 2** Characteristics of pediatric MH admissions

| Characteristic | NIS/KID 1998–2010 *n* = 56.43 (%)[a] | Admissions with MH *n* = 310 (%) |
|---|---|---|
| Sex, male | 23.9 (42.4) | 201 (64.8) |
| Age, years | | |
| <1 | 11.58 (20.5) | 32 (10.3) |
| 1–3 | 1.66 (2.9) | 88 (28.4) |
| 4–11 | 1.88 (3.3) | 86 (27.7) |
| 12–17 | 2.66 (4.7) | 104 (33.5) |
| Race | | |
| White | 26.59 (47.1) | 137 (58.3) |
| Black | 5.93 (10.5) | 29 (12.34) |
| Hispanic | 5.37 (9.5) | 41 (17.5) |
| Asian | 3.05 (5.4) | 7 (3.0) |
| Native American | 0.17 (0.4) | 2 (0.9) |
| Other | 1.20 (2.1) | 19 (8.1) |
| Unknown | 14.11 (25.0) | 75 (24.2) |
| Hospital of admission [b] | | |
| Not a children's hospital | 8.24 (68.4) | 70 (38.5) |
| General children's hospital | 0.98 (8.1) | 33 (18.1) |
| Specialty children's hospital | 0.02 (0.1) | 2 (1.1) |
| Children's unit in general hospital | 2.05 (17.1) | 61 (33.5) |
| Unknown | 0.75 (6.3) | 16 (8.8) |

[a]number in millions and rounded to the nearest ten thousand.
[b]Only the cases extracted from KID (*n* = 12,039,432 for all and *n* = 182 for MH) were used because 'Hospital of Admission' is not recorded in NIS.

Comorbidities included in the admissions, total and pediatric, were hereditary progressive muscular dystrophy, congenital hereditary muscular dystrophy, arthrogryposis, disorders of mitochondrial metabolism, and heat stroke. A number of previously defined associations were not present in this analysis (3,4,6). (Table 3).

Univariate and multivariate regression with the outcome of mortality did not yield significant differences between demographic factors, age, sex, race, or hospital type, pediatric vs nonpediatric. (Table 4) Associations between mortality and other comorbidities were limited due to a low number of deaths. A total of 530 449 admissions had an additional ICD-9 code describing a surgical procedure in the KID dataset. From these, 55 had the code for MH, with a calculated rate of 1.04 cases per 10 000 pediatric surgical admissions.

**Table 3** Number of pediatric admissions with associated diagnoses and comorbidities

| ICD-9 code | NIS/KID 1998–2010 *n* = 56 424 869 (%) | Admissions with MH *n* = 310 (%) |
|---|---|---|
| Associated diagnoses | | |
| Rhabdomyolysis (728.88) | 55 575 (0.10) | 26 (8.4) |
| Sepsis (995.91) | 174 706 (0.31) | 10 (3.2) |
| Comorbidities | | |
| Hereditary progressive Muscular dystrophy (359.1) | 17 138 (0.03) | 5 (1.6) |
| Congenital hereditary muscular dystrophy (359.0) | 2678 (0.005) | 6 (1.6) |
| Arthrogryposis (728.3 &754.82) | 10 426 (0.02) | 5 (1.4) |
| Disorders of mitochondrial metabolism (277.87) | 3432 (0.006) | 4 (1.1) |
| Heat stroke (992.0) | 2689 (0.005) | 3 (0.8) |

No MH admissions had the comorbidities of HIV disease (042), infective myositis (728.0), dermatomyositis (710.3), strabismus (378.0 and 378.60), neuroleptic malignant syndrome (333.92), hypoxic–ischemic encephalopathy (768.7), thyrotoxicosis (242.0), periodic paralysis (359.3), and pneumonia due to influenza (487.0), parainfluenza (480.2), or adenovirus (480.0).

## Discussion

The present study is the first to combine two major national databases to examine the number of pediatric patients diagnosed with malignant hyperthermia from 1998 to 2010 in the United States. Our purpose was to develop a more clear understanding of the incidence, risk factors, and morbidity and mortality associated

**Table 4** Multivariate logistic regression of mortality in pediatric admissions with MH on KID dataset

| Variable[a] | Univariate | | | Multivariate[b] | | |
|---|---|---|---|---|---|---|
| | OR | *P* | 95% CI | OR | *P* | 95% CI |
| Age | 1.1 | 0.26 | 0.94–1.25 | 1.03 | 0.65 | 0.89–1.20 |
| Sex, female | 0.38 | 0.38 | 0.04–3.30 | 0.41 | 0.44 | 0.04–3.92 |
| Race, nonwhite | 5.05 | 0.15 | 0.55–46.46 | 4.87 | 0.16 | 0.52–45.24 |
| Hospital type, nonchildren's | 0.84 | 0.10 | 0.68–1.03 | 0.64 | 0.65 | 0.10–4.18 |

[a]Age is a continuous variable, reference zero.
[b]Adjusting for age, sex race, and hospital type.

with admissions containing an ICD-9 diagnosis of malignant hyperthermia in the pediatric population. The analysis identified 310 admissions for patients <18 years of age with a diagnosis of MH. Children 12–17 years of age comprised a small percentage of admissions (4.7%) in the combined database of NIS and KID, but represented the largest group (33.5%) admitted with MH in the KID database. Nine of the children admitted died representing 2.9% of the total patients with a diagnosis of MH. This was notably different than other reports with similar methodology; Rosero *et al*. reported a mortality rate of 0.7% (6), while Li *et al*. had 4.6% (3). However, grouping mortality rates by age found the pediatric category among the combined database to have the lowest death rate compared to adults 18.2%. Yet more concerning was the increase in the total death rate to 15.1% in patients with a diagnosis of MH reflecting a 29% increase compared to the 11.7% mortality rate reported in the study by Rosero *et al*. (6) for the years 2000–2005.

The 310 pediatric admissions identified in this study represented 20% of all MH admissions from both databases. This is a greater proportion of children than the 17.8% reported by Rosero *et al*. (6), but less than the 45% reported by Larach *et al*. (4), although the differences may be attributed to sampling size and method. Caucasian patients (58.3%) comprised the majority of MH admissions, and Hispanic children (17.5%) represented the second most common group. Examination of gender differences found 64.8% or almost twice as many boys diagnosed with MH compared to girls, which was consistent with the previous KID study(3) and greater than reported in the NIS study (6). The male predominance was reflected in the study of MH in New York state along with a significantly higher mortality rate of 22% (7). Also, the authors in the NIS study found females to be at significantly higher risk of death (6), while there were no significant differences identified in this study (univariate logistic regression, OR 0.38, 95% CI 0.04–3.30).

The database was also queried for the effects of comorbidities and type of treatment facility on patient mortality. Most children with MH received care at a children's unit or pediatric designated hospital (52.7%). Unadjusted and adjusted logistic regression analysis did not yield any statistically significant findings in relation to variables such as age, gender, and race when assessing for the outcome of death. In addition, comparison of outcomes between children seen at a pediatric hospital or unit vs nonchildren's hospital demonstrated no significant difference in mortality.

The database was queried for children with a discharge diagnosis of MH who underwent one of the 500 most common noncardiac operations as listed by the American College of Surgeons Pediatric National Surgical Quality Improvement Program. Fifty-five surgical admissions with MH were identified. The prevalence of MH among patients with a concomitant ICD-9 coding for a surgical procedure was 1.04 per 10 000. The only reported pediatric death from surgical admissions with the diagnosis of MH was associated with patients having the diagnosis of rhabdomyolysis, possibly as a marker of more severe disease. Muscular dystrophies represented the largest comorbidity reported among those admitted with MH although this may represent miscoding due to the similar clinical presentation. Other disorders thought at one time to be associated with MH were found to have strong associations, but the number of actual cases made the findings inconclusive. However, the lack of association with other comorbidities should not exclude this possibility, because it may be more a reflection of the dataset.

There was no statistically significant association between demographic variables, such as age, gender, race or type of hospital, and the diagnosis of MH.

Comparison to previous studies of the NIS and KID was mixed. The NIS study by Rosero *et al*. identified 454 admissions <18 years of age with three inhospital deaths, while this study identified 310 with nine deaths (6). The difference is mainly due to the use of weighted numbers by Rosero, while this report shows crude numbers that are less affected by the possible oversampling of low-mortality centers. The presence of musculoskeletal and connective tissue disorders was noted for both KID studies and in particular muscular dystrophies.

There are several limitations to our study. As in every analysis performed in administrative databases, there is a risk of miscoding, but as the ICD-9 coding is extracted from billing records, we presume that this is relatively controlled although there may have been some patients that received the MH code just on the basis of family history. Associated comorbidities, such as mitochondrial disorders or muscular dystrophy, are at increased risk of miscoding due to their similar clinical presentation. Our entries are not necessarily patients, but admissions. This means that a single patient may translate into multiple entries if admitted multiple times, and MH was coded as a relevant diagnosis even though there was no exposure to a general anesthetic. We attempted to control this with our prevalence calculation by just including surgical admissions. Also, temporality and causality cannot be ascertained; therefore, comorbidities may be present before or after the diagnosis of MH. This is especially important as comorbidities and mortality can only be associated with an MH diagnosis but not attributed to. Ten of the 14 years included in this

 

report were extracted from NIS. NIS samples by selecting hospitals and then includes patients within those hospitals, potentially over or under sampling centers were MH patients may concentrate. We attempted to ameliorate the risk of selective sampling by including KID, which samples by directly selecting patients and includes a much larger frame of hospitals than NIS. Overall, 182 of our 310 pediatric admissions came from KID. These and other limitations previously delineated by Memtsoudis should be considered when interpreting our results (8). Despite these, we believe that our study, with its relatively large cohort of admissions with the diagnosis of MH, remains valid. Obtaining a similar sample size and critically review their medical charts will be a next step to better understand MH in children, but a considerable effort will be required to identify a significant number of patients with this rare disease. We have attempted to maximize the benefits that NIS and KID can offer, obtain the most information possible from these admissions, and present in a way that has clinical relevance for anesthesiologists and clinicians that treat children.

In summary, analysis of the combined database of the Nationwide Inpatient Sample and the Kids' Inpatient Database yielded insight into the prevalence of MH in the pediatric population in the United States and the associated risk factors for morbidity and mortality. There were 310 cases of MH identified in the 0–17-year-old age range with a mortality rate of 2.9% and an overall mortality rate of 15.1% for all patients. The mortality rate for adults was 18.2%, which was 30% greater than that reported by Rosero *et al.* (6) for the 18–65+ age group. The explanation for this discrepancy requires further study and is beyond the scope of this paper. The most common relevant diagnosis associated with pediatric MH cases was rhabdomyolysis. Other comorbidities associated with MH were few in number or not identified during the review of pediatric admissions with MH. Statistical analysis of age, gender, race, or type of hospital facility as risk factors associated with mortality did not achieve significance. Malignant hyperthermia in the pediatric population represents 20% of cases, which is significantly less than previous reports; however, the prevalence of MH among children with a concomitant ICD-9 coding for a procedure was 1.04 per 10 000. Until proper epidemiologic studies are done, the use of databases will continue to be the optimal method to study rare diseases.

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Ethical approval: The study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

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## Conflict of Interest

Tae W. Kim—MH Hotline Consultant for the Malignant Hyperthermia Association of the United States.

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