

REVIEW

Anesthesia-related mortality in pediatric patients: a systematic review

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This systematic review of the Brazilian and worldwide literature aimed to evaluate the incidence and causes of perioperative and anesthesia-related mortality in pediatric patients. Studies were identified by searching EMBASE (1951-2011), PubMed (1966-2011), LILACS (1986-2011), and SciELO (1995-2011). Each paper was revised to identify the author(s), the data source, the time period, the number of patients, the time of death, and the perioperative and anesthesia-related mortality rates. Twenty trials were assessed. Studies from Brazil and developed countries worldwide documented similar total anesthesia-related mortality rates (<1 death per 10,000 anesthetics) and declines in anesthesia-related mortality rates in the past decade. Higher anesthesia-related mortality rates (2.4-3.3 per 10,000 anesthetics) were found in studies from developing countries over the same time period. Interestingly, pediatric perioperative mortality rates have increased over the past decade, and the rates are higher in Brazil (9.8 per 10,000 anesthetics) and other developing countries (10.7-15.9 per 10,000 anesthetics) compared with developed countries (0.41-6.8 per 10,000 anesthetics), with the exception of Australia (13.4 per 10,000 anesthetics). The major risk factors are being newborn or less than 1 year old, ASA III or worse physical status, and undergoing emergency surgery, general anesthesia, or cardiac surgery. The main causes of mortality were problems with airway management and cardiocirculatory events. Our systematic review of the literature shows that the pediatric anesthesia-related mortality rates in Brazil and in developed countries are similar, whereas the pediatric perioperative mortality rates are higher in Brazil compared with developed countries. Most cases of anesthesia-related mortality are associated with airway and cardiocirculatory events. The data regarding anesthesia-related and perioperative mortality rates may be useful in developing prevention strategies.

KEYWORDS: Anesthesia; Cardiac Arrest; Mortality; Perioperative; Pediatric; Review.

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INTRODUCTION

Studies have revealed that there is a higher perioperative mortality rate in children compared with adults (1-4). Within the pediatric population, perioperative mortality is more frequent in neonates and infants compared with older children (2,3,5-8).

An analysis of overall perioperative mortality and anesthesia-related mortality in particular may help determine which children are at higher risk and may help guide planning to improve the safety profile of perioperative techniques.

Large-scale and national studies of anesthesia-related mortality in children have been performed in a number of countries (3,5,9-11). In Brazil, there have been three studies

on pediatric perioperative mortality (12-14), but no nationwide study has been undertaken.

The aim of the present review was to perform a systematic review of the Brazilian and worldwide literature to evaluate the incidence and causes of perioperative and anesthesia-related mortality in pediatric patients.

METHODS

We performed a text word search strategy to identify cross-sectional studies of perioperative and/or anesthesia-related mortality in children using the following words: "cardiac arrest", "mortality" and "anesthesia" (classified according to MeSH terms). Studies were obtained from EMBASE (1951-2011), the US National Library of Medicine (PubMed, 1966-2011), LILACS (1986-2011), and the Scientific Electronic Library Online (SciELO, 1995-2011). We also used the "related articles" function on PubMed and the references cited in the studies found in the database searches. The present review was completed in October 2011. There was no language restriction since the publications included an abstract written in English and if the studies used the original data to suggest a perioperative cardiac arrest and/or

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mortality rate that was related to anesthetic management in a pediatric patient population (at least 5,000 cases of anesthetic use) over a defined period. Some studies included pediatric and adult patients; however, we only reported the mortality incidence of the pediatric population (the mortality rate = the number of deaths x 10,000/ the number of children who were anesthetized). Studies were excluded if the anesthetic management was limited to a particular technique, surgery, associated disease state, or within a specific pediatric age group. Other studies on anesthesia-related cardiac arrest and/or mortality that offered additional relevant information were also examined.

Mortality-triggering factors were assigned to one of the following groups: surgery-related, related to patient disease or condition, and anesthesia-related. Three reviewers independently screened the titles that were identified in the literature search, extracted the data, and analyzed the results. Discrepancies in the results were resolved by discussion. A standard form was used to extract the following information: the author(s), the data source, the time period, the number of pediatric patients, the time of death (i.e., in the operating room, during recovery from anesthesia, during the first 12 or 24 postoperative hours, and within seven or eight postoperative days), the perioperative mortality rate (including

all mortality-triggering factors), the anesthesia-related mortality rate, the type of anesthesia, the American Society of Anesthesiologists (ASA) physical status, the patients' ages, and the factors that contributed to mortality.

RESULTS

The database queries identified 20 articles that reported perioperative and anesthesia-related cardiac arrest or mortality data in children: 17 of these articles were from international investigators, and three were from Brazilian investigators (Tables 1 and 2).

A comparison of the data reported by investigators from developed countries worldwide between 1961 and 2000 with papers published between 2001 and 2011 demonstrated that anesthesia-related mortality rates declined from 0.2-2.9 per 10,000 anesthetics (9,10,15-17) for the forty-year period ending in 2000 (Table 1) to 0.0-0.69 per 10,000 anesthetics (6,8,18-20) for the ten-year period ending in 2011 (Table 2). In Brazil, one study performed during the latter period reported an anesthesia-related mortality rate of 0.0 per 10,000 anesthetics (14), which was similar to the rates reported by the studies in developed countries (Table 2). The highest anesthesia-related mortality rates (2.4 to 3.3 per

Table 1 - Mortality incidence in pediatric patients who underwent anesthesia between 1961 and 2000.

| Investigators and Year of Publication | Time Period and Data Source | Number of Patients and Time of Death | Age | Mortality Incidence per 10,000 Anesthetics | |
|---------------------------------------|--|--|---------|--|--------------------|
| | | | | Perioperative | Anesthesia-related |
| Rackow et al. (1961) (15) | 1947-1956 Teaching hospital USA | 34,499 Deaths in OR and PACU | ≤12 y | 4.9 | 2.9 |
| Keenan & Boyan (1985) (16) | 1969-1983 Teaching hospital USA | 12,712 Deaths within 8 days | ≤11 y | NR | 1.57 |
| Tiret et al. (1988) (9) | 1978-1982 Group of 440 hospitals France | 40,240 Deaths within 24 h | ≤14 y | NR | 0.2 |
| Cohen et al. (1990) (21) | 1982-1987 Teaching hospital Canada | 29,220 Deaths in OR and PACU | ≤16 y | 3.8 | NR |
| | | | <1 mo | 83.1 | |
| | | | 1-12 mo | 7.9 | |
| | | | 1-5 y | 3.0 | |
| | | | 6-10 y | 1.4 | |
| | | | 11-16 y | 1.8 | |
| Aubas et al. (1991) (17) | 1983-1987 Teaching hospital France | 16,207 Deaths in OR and PACU | ≤14 y | NR | 1.23 |
| | | | 0-4 y | | 2.3 |
| | | | 5-14 y | | 0 |
| Conceição & Costa (1995) (12) | 1980-1993 Teaching hospital Brazil | 30,028 Deaths within 24 h | ≤12 y | 0.33 | NR |
| Cicarelli et al. (1998) (13) | 1995 Teaching hospital Brazil | 7,392 Deaths within 24 h | ≤12 y | 5.4 | NR |
| Murray et al. (2000) (10) | 1994-1997 Group of hospitals USA, Canada | 1,089,200 (estimated) Deaths in OR and PACU | ≤18 y | NR | 0.36 |

OR = operating room; PACU = postanesthesia care unit; NR = not reported.

Table 2 - Mortality incidence in pediatric patients who underwent anesthesia between 2001 and 2011.

| Investigators and Year of Publication | Time Period and Data Source | Number of Patients and Time of Death | Age | Mortality Incidence per 10,000 Anesthetics | |
|---------------------------------------|---|--|--|--|--|
| | | | | Perioperative | Anesthesia-related |
| Biboulet et al. (2001) (18) | 1989-1995 Teaching hospital France | 23,832 Deaths within 12 h Excluded: ASA V patients | ≤14 y 0-4 y 5-14 y | NR | 0.42 0 0.84 |
| Morita et al. (2001)* (3) | 1999 Group of hospitals Japan | 732,788 (adults and children) Deaths within 7 days | <1 mo <12 mo <5 y <18 y | 42.75 2.95 2.54 1.7 | 0 0 0 0.17 |
| Tay et al. (2001) (22) | 1997-1999 Teaching hospital Singapore | 10,000 Deaths in OR and PACU | NR | 3.0 | 0 |
| Morita et al. (2002)* (5) | 2000 Group of hospitals Japan | 910,757 (adults and children) Deaths within 7 days | <1 mo <12 mo <5 y <18 y | 18.86 4.6 1.26 1.57 | 0 0 0.21 0.14 |
| Newland et al. (2002) (19) | 1989-1999 Teaching hospital USA | 16,051 Deaths within 24 h | ≤20 y | NR | 0 |
| Murat et al. (2004) (20) | 2000-2002 Teaching hospital France | 24,165 Deaths within 24 h Excluded: neurosurgery and cardiac surgery | ≤16 y 0-<1 y 1-7 y 8-16 y | 0.41 2.71 0 0 | 0 |
| Braz et al. (2006) (14) | 1996-2004 Teaching hospital Brazil | 15,263 Deaths in OR and PACU | ≤17 y | 9.8 | 0 |
| Flick et al. (2007) (6) | 1998-2005 Teaching hospital USA | 92,881 Deaths in OR and PACU | <18 y 0-30 days 31 days-<1 y 1-3 y 4-9 y 10-<18 y | 6.8 144.7 19.2 5.7 3.1 2.1 | 0.21 0 0 0 0.39 0.26 |
| Ahmed et al. (2009) (23) | 1992-2006 Teaching hospital Pakistan | 20,216 Deaths in OR Excluded: cardiac surgery | ≤18 y 0-1 y >1-18 y | 3.46 11.43 1.26 | 0.49 2.28 0 |
| Bharti et al. (2009) (7) | 2003-2008 Teaching hospital India | 12,158 Deaths within 48 h Excluded: eye and cardiac surgeries | ≤17 y 0-<1 y 1-<4 y 4-<10 y 10-17 y | 10.7 18.5 6.3 6.5 9.1 | 3.3 4.7 0 2.5 0 |
| Bunchungmongkol et al. (2009) (11) | 2003-2004 Group of hospitals Thailand | 25,098 Deaths within 24 h | ≤15 y 0-1 y >1-8 y >8-15 y | 15.9 35.1 9.4 12.2 | 2.4 3.7 0.9 3.3 |
| van der Griend et al. (2011) (8) | 2003-2008 Teaching hospital Australia | 101,885 Deaths within 24 h | ≤18 y 0-30 days 31 days-<1 y 1-<4 y 4-<10 y 10-18 y | 13.4 180.1 32.2 6.6 3.4 5.9 | 0.69 3.51 0.80 1.11 0.31 0.36 |

OR=operating room; PACU=postanesthesia care unit; NR=not reported.

*Japanese text: the information was obtained from the English abstract (the number of children anesthetized was not reported in the abstract).

10,000 anesthetics) were observed in the studies that were performed in the developing countries (7,11) between 2001 and 2011 (Table 2).

An analysis of the data that were reported by the investigators from the developed countries showed perioperative mortality rates ranging from 3.8 to 4.9 per 10,000

anesthetics (15,21) from 1961-2000 (Table 1) to 0.41-13.4 per 10,000 anesthetics (6,8,20) from 2001-2011 (Table 2). In the developing countries, the perioperative mortality rates from 2001-2011 ranged from 3.0 to 15.9 per 10,000 anesthetics (7,11,22,23) (Table 2). A comparison of the Brazilian data that was reported between 1961 and 2000 with data from 2001-2011 showed that perioperative mortality rates ranged from 0.33 to 5.4 per 10,000 anesthetics (12,13) during the former period to 9.8 per 10,000 anesthetics (14) during the latter period (Tables 1 and 2, respectively).

In studies from both developing (7,11,23) and developed (3,5,6,8,17,21) countries, the mortality rates were higher in newborns and children under one year of age compared with older children.

An ASA physical status of III or greater (6-9,11,14,19) and emergency surgery (6,7,14,23,24) were risk factors for pediatric perioperative mortality. Studies from developing countries verified anesthesia-related mortality in ASA physical status I-II children (7,11). Although one study (7) found that female children had a greater risk of cardiac arrest and another study (11) found that male children had a greater risk of cardiac arrest, other studies have shown that gender is not a risk factor for mortality in children (6,14). In some studies (14,23), the patient's condition or disease represented the major perioperative mortality-triggering factor, with surgery and anesthesia being the next most important factors. Interestingly, other studies (8,25,26) have indicated that complications associated with cardiac procedures are the major cause of pediatric perioperative mortality.

Regarding the type of anesthesia, higher rates of perioperative cardiac arrest and mortality have been reported in patients who underwent general anesthesia compared with patients who underwent neuraxial anesthesia (7,10,14,23).

Many studies have found that respiratory and cardiovascular causes contribute equally to the cases of cardiac arrest and mortality that occur in children during anesthesia (16,27). In some studies, respiratory causes of cardiac arrest and mortality in children were more frequent than cardiovascular causes (7,11,14,20,23,25). In other studies, however, cardiovascular effects were reported to be the major factor that contributed to anesthesia-related mortality (10,19,24,28,29). The administration of anesthetic drugs and inadequate blood management during hemorrhage and anemia were the most frequent causes of cardiovascular effects (10).

DISCUSSION

There is no consensus in the literature regarding the definition of anesthesia-related mortality (30). Attributing death to anesthesia is difficult and often relies on the subjective interpretation of various definitions. The North American Pediatric Perioperative Cardiac Arrest (POCA) Registry classifies cardiac arrest as anesthesia-related if anesthesia personnel or the anesthetic process played at least some role (the role can range from minor to major) in the cause of the cardiac arrest (10). The Australian and New Zealand College of Anaesthetists Mortality Committee has classified anesthesia-related mortality into 3 categories: category 1 includes cases in which it is reasonably certain that death was caused by anesthesia or other factors under the control of the anesthetist, category 2 is used when there

is some doubt as to whether death was entirely attributable to the anesthesia or other factors under the control of the anesthetist, and category 3 applies when death was caused by both surgical and anesthetic factors (31). The existence of these differences shows that there is an urgent need for a consensus when defining "anesthesia-related mortality" (30). Further improvements will depend on international multispecialty efforts to standardize the terminology (32).

Other substantial differences in methodology make it difficult to compare anesthesia-related mortality rates among various studies. In the studies in which perioperative and anesthesia-related mortality in children have been examined (3,5-23), the definition of deaths in which anesthesia was the primary cause or a contributing cause have varied widely among the investigators, as did the time window that was considered to be the perioperative period. The perioperative period has been defined as intraoperative only (23), intraoperative through the recovery from anesthesia (6,10,14,15,17,21,22), the first 12 postoperative hours (18), the first 24 postoperative hours (8,9,11-13,19,20), two postoperative days (7), and 7-8 postoperative days (3,5,16). Although the majority of the studies of anesthesia-related mortality are cross-sectional (3,5-9,11-23), several studies are based on voluntary declarations of critical incidents (10). Furthermore, the mortality rate may depend on the surgical pediatric population. Several studies have examined all types of surgery (3,5,6,8,10-17,21,22), whereas other studies have excluded procedures in ASA V patients (18), cardiac surgery (7,20,23), eye surgery (7), or neurosurgery (20). Some studies have included children up to 12 years of age (12,13,15), whereas other studies have also included children from 14 to 17 (3,5-7,9,11,14,17,18,20,21) or from 18 to 20 years of age (8,10,19,23).

Despite these differences in methodology, studies undertaken in a variety of countries, including Brazil, have suggested that anesthesia-related mortality rates in children are lower today than they were 50 years ago. The pioneering study by Rackow et al. (15), which covered the period from 1947-1956, reported an anesthesia-related mortality rate in children of 2.9 per 10,000 anesthetics. Most studies that have been published over the past decade have reported an overall pediatric anesthesia-related mortality rate of less than 1 per 10,000 anesthetics, which represents a threefold improvement (6,8,18-20,22,23). One Brazilian study has confirmed this trend (i.e., zero anesthesia-related deaths per 10,000 anesthetics) (14). Multiple factors, including safer anesthetic agents, better monitoring devices and the development of a specialized pediatric environment, have contributed to this improvement. However, surveys of anesthesia-related mortality conducted in certain developing countries between 2001 and 2011 have reported higher anesthesia-related mortality rates (i.e., 2.4 to 3.3 per 10,000 anesthetics) (7,11). According to Lagasse (33), the higher mortality rates that have been reported in these studies could either represent real differences in anesthesia safety or differences in the tools that were used to measure anesthesia-related mortality.

In contrast to the apparent decrease in anesthesia-related mortality in children over the last decade, the majority of studies conducted in developed (6,8,15,21) and developing countries (7,11,22,23), including Brazil (14), have suggested that perioperative pediatric mortality has not decreased in the last decade. Worldwide, even higher perioperative

(3,5-8,11,20,23) and anesthesia-related mortality rates (7,11) have been reported for neonates and infants. Prematurity, congenital heart disease, congenital neurological disease, and other congenital defects place neonates and infants at a higher anesthesia risk compared with older children and adults (10). The incidence of respiratory events during anesthesia is also higher in younger children (20). This effect may be due to the relatively narrow infant airway and the higher incidence of respiratory tract infections in young children (34,35). The findings of increased risk for children who are younger than 1 year of age (especially children younger than 1 month) indicate the need for greater caution when caring for children who are under 1 year of age (30).

Poor ASA physical status (\geq III) and emergency surgery have been reported as risk factors for pediatric perioperative mortality and are the only predictive factors of mortality after cardiac arrest (8,10). Morita et al. (3) found that most incidents of perioperative cardiac arrest and death in neonates can be attributed to underlying comorbidities rather than causes related to the anesthesia. Children with heart disease exhibit higher rates of perioperative cardiac arrest and mortality when undergoing cardiac (8,25,26) or noncardiac surgery (8,36).

In addition, with the advent of sophisticated extracorporeal cardiorespiratory support systems and specific medical therapies, children with highly complex medical problems who were once considered unfit for anesthesia are increasingly submitted to surgery and other procedures, including medical imaging (8). Pre-existing morbidities, such as sepsis, are also important factors in perioperative cardiac arrest in children both in Brazil (14) and in other developing countries (7). Flick et al. (6) have reported an overall perioperative mortality rate for children in the United States of 6.8:10,000 anesthetics. In the Flick et al. study, the mortality rate associated with cardiac surgery was 115.5 per 10,000 anesthetics, whereas the mortality rate associated with noncardiac surgery was 1.6 per 10,000 anesthetics. A recent study conducted in Australia, performed by van der Griend et al. (8), reported a high overall perioperative mortality rate in children (13.4 per 10,000 anesthetics). For cardiac surgery, the associated mortality rate was 127.1 per 10,000 anesthetics, and the rate for noncardiac surgery was 8.2 per 10,000 anesthetics. The same authors proposed a new definition of anesthesia-related death that includes all cases in which it is more likely than not that factors that are related to anesthesia and are under the control of the anesthesiologist influenced the timing of death. This definition does not imply that care was inadequate or negligent. The use of this definition may explain the higher pediatric mortality rates reported by van der Griend et al. (8) with a recent study in the USA (6). Indeed, it seems likely that the exclusion of cardiac surgery patients (7,20,23) or children with a poor ASA physical status (18) has a significant impact on the estimated pediatric perioperative mortality rate. There were no anesthesia-related deaths in children without significant comorbidities (8). These results imply that the anesthesia-related mortality rate in healthy children is not a great indicator for assessing the quality of care. The results also imply that when seeking routine consent for anesthesia and when discussing anesthesia risk, the risk of death may not be a concern for children who do not have significant comorbidities. This statement, however,

requires some caution because anesthesia-related mortality still occurs in ASA physical status I-II children (7,11).

The POCA Registry was formed by the ASA in 1994 (10). This registry includes 63 participating institutions in the USA and Canada, most of which are tertiary referral centers. Each of the institutions in the registry submits a standardized data form for each case of cardiac arrest that occurs in a child younger than 18 years old during the intraoperative period or while the patient is in the postanesthesia care unit. The POCA Registry has documented that the medication-related cardiac arrest rate in children decreased from 37% between 1994 and 1997 to 18% between 1998 and 2004 (24). This decrease was attributed to the increased use of sevoflurane, which is an anesthetic that has been reported to have a lower potential than halothane for inducing bradycardia (37) and myocardial depression (38) in infants and children. According to the POCA Registry, cardiovascular causes were the most common causes of cardiac arrest and were associated with 41% of all cardiac arrests in the period between 1998 and 2004. Hypovolemia from blood loss and hyperkalemia from the transfusion of stored blood were the most common cardiovascular causes of cardiac arrest. Respiratory causes accounted for 27% of all cardiac arrests, with airway obstruction from laryngospasm being the most common cause. In the present report, mortality after anesthesia-related cardiac arrest was 28%, which was similar to the 26% that was initially reported by the POCA Registry (10). As acknowledged by Morray et al. (10), however, the POCA Registry's assessment of the frequency of cardiac arrest in children during and after surgery has several methodological limitations. The most significant is the potential for underreporting in this voluntary system. Selection bias is also likely, and more sensitive cases may not always be reported.

Mortality due to ventilation problems has decreased since the 1990s because of advanced respiratory monitoring and the introduction of laryngeal mask airway devices for neonates and children. Interestingly, cardiovascular events have joined ventilatory problems as the major risk sources for anesthesia-related pediatric cardiac arrest and death in developed countries (10,19,29). In the 2000s, respiratory events were still the main cause of anesthesia-attributable cardiac arrests in Brazil (14), other developing countries (7,11,23), and even in the USA (6).

In a study of 532 cases from the ASA's Pediatric Closed Claims, the proportion of claims due to death/brain damage and respiratory-related damaging events, particularly those associated with inadequate ventilation/oxygenation, decreased between 1973 and 2000 (29). However, claims due to death (47%) and brain damage (21%) constituted the largest proportion of the claims made in the 1990s. During the last period, cardiovascular events (26%) joined respiratory events (23%) as the major sources of liability. This trend may be related to the increased use of pulse oximetry and end-tidal carbon dioxide monitoring and to the introduction of sevoflurane. The Jimenez et al. study also reported that an ASA physical status of III-IV was associated with an increased frequency of claims due to death and brain damage compared with claims for less severe injuries.

The incidence of perioperative cardiac arrest and mortality in children is higher during general anesthesia compared with neuraxial anesthesia (7,10,14,23). Morray et al. (10)

examined data from the POCA Registry and observed that in most cases of anesthesia-related cardiac arrest, only general anesthesia was administered (88%). This finding may not be surprising because many pediatric high-risk surgeries, including cardiac, thoracic, and neurosurgical procedures, are performed under general anesthesia. In addition, improved knowledge of neuraxial block physiology and the use of newer, safer local anesthetics in combination with the routine use of oxygen according to pulse oximetry values have decreased major complications during neuraxial anesthesia.

A monitoring period in the postanesthesia care unit is now mandatory following all types of anesthesia. For high-risk children, continued monitoring in a pediatric intensive care unit may reduce anesthetic-related mortality. The inability to provide or the failure to use these facilities may increase anesthesia-related mortality rates.

Pediatric anesthesia requires trained pediatric anesthesiologists or trainees who are supervised by a consultant pediatric anesthesiologist. Anesthesia-related mortality may differ between centers that primarily include staff who are trained in pediatric anesthesiology and centers with fewer specifically trained staff (8). In addition, continuing education for pediatric anesthesiologists is highly recommended. Indeed, one study demonstrated that the poor practical application of techniques rather than a lack of knowledge can lead to critical incidents (39).

The present review had some methodological weaknesses. Because of the temporal limitations of the databases, it was difficult to verify that all of the relevant studies that predated the EMBASE (1951) and Medline databases (1966), and even certain studies from after these dates, were considered.

Our systematic review of the literature confirms that pediatric anesthesia-related mortality rates in Brazil over the last decade are similar to those in developed countries. Higher pediatric anesthesia-related mortality rates over the same time period have been found in some studies from developing countries. Pediatric perioperative mortality rates have not decreased in the previous decade and are higher in Brazil and other developing countries compared with developed countries. The major risk factors for anesthesia-related mortality are age (i.e., newborns or infants less than 1 year old have the greatest risk), ASA III or worse physical status, emergency surgery, general anesthesia, and cardiac surgery. Airway management problems and cardiocirculatory events accounted for the majority of the cases of anesthesia-related mortality in children with comorbidities. These data may be useful in developing prevention strategies to prevent anesthesia-related deaths in pediatric patients.

AUTHOR CONTRIBUTIONS

Gonzalez LP and Braz JRC were responsible for the study design, the data analysis, and manuscript writing. Pignaton W, Kusano PS, and Mólolo NSP were responsible for the data analysis and the approval of the final version of manuscript. Braz LG was responsible for the study design, data analysis, manuscript writing, and archiving of the study files.

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