Discrepancies Between Clinical Diagnoses and Autopsy Findings in Critically Ill Children

A Prospective Study

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ABSTRACT

Objectives: *To evaluate the discrepancies between clinical and autopsy diagnoses in patients who died in the pediatric intensive care units (PICUs) of a tertiary care university hospital.*

Methods: *A prospective study of all consecutive autopsies discussed at monthly mortality conferences over 5 years. Discrepancies between premortem and autopsy diagnoses were classified according to modified Goldman et al criteria.*

Results: *From January 1, 2011, to December 31, 2015, a total of 2,679 children were admitted to the two PICUs of our hospital; 257 (9.6%) died, 150 (58.4%) underwent autopsy, and 123 were included. Complete concordance between clinical and postmortem diagnoses was observed in 86 (69.9%) patients; 20 (16.3%) had a class I discrepancy, and eight (6.5%) had a class II discrepancy. Comparing 2011 and 2015, the rate of major discrepancies decreased from 31.6% to 15%.*

Conclusions: *Our results emphasize the importance of autopsy to clarify the cause of death and its potential contribution to improvement of team performance and quality of care.*

CME/SAM

Upon completion of this activity you will be able to:
- apply the modified Goldman criteria to classify discrepancies between premortem diagnoses and autopsy findings.
- list the most prevalent clinical causes of death in the pediatric intensive care unit.
- describe the main unsuspected causes of death revealed by autopsy in postoperative cardiac surgery patients.
- discuss the importance of autopsy as an educational tool to improve team performance.

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The autopsy is considered the gold-standard method for evaluating accuracy of clinical diagnoses and plays an important role in quality control of medical care and education.[1] Despite advances in diagnostic techniques and therapeutic interventions, autopsy studies of critically ill adults and children have shown that even in the modern medical era, clinicopathologic discrepancies still exist.[2-5] By accurately determining the cause of death, revealing new or unexpected findings and possible diagnostic or technical errors, postmortem examinations can significantly

contribute to improvement of team performance and quality of care. To our knowledge, no published studies have compared clinical and autopsy findings in critically ill children who died in the past decade. We aimed to evaluate the accuracy of clinical diagnoses compared with autopsy findings in critically ill children who died over the past 5 years in the pediatric intensive care units (PICUs) of a tertiary care university hospital in Brazil.

Materials and Methods

This is a prospective study of all consecutive autopsies performed on patients who died in two medical-surgical PICUs (total beds = 18) in a tertiary care university hospital in Brazil between January 1, 2011, and December 31, 2015. The study was approved by the institutional research ethics board of the Hospital das Clínicas of Ribeirão Preto Medical School, University of São Paulo (2451/2011). Permission to perform an autopsy was requested from the families of all patients who died in the PICU by attending physicians or residents. Patients who became organ donors and forensic cases were excluded from the study. Six to 20 hours after death, thorough autopsies were performed by a pathology resident under supervision of a senior pathologist (F.S.R.) from the Department of Pathology of our institution. All organs were inspected ex situ, when tissue samples were collected for histopathologic examinations. Additional histochemistry, immunohistochemistry, and molecular techniques were employed when required. All clinical, laboratory, and imaging data were available to the pathologists at the time of autopsy.

Demographic and clinical data were collected every month from the patients' health records, including age, sex, length of PICU stay, clinical diagnoses, laboratory results, imaging data, and clinical cause of death. Macroscopic and microscopic autopsy findings and the clinical diagnosis of the causes of death were discussed at the monthly mortality conferences traditionally held at our institution at which data are reviewed and the previous month's PICU deaths are discussed.

Discrepancies between premortem and autopsy diagnoses were classified according to modified Goldman et al[6] criteria.[3] Class I errors comprised major misdiagnoses that, if known before death, probably would have changed treatment, which could have resulted in improved survival or cure. Class II diagnostic errors were defined as major unexpected findings for which detection before death probably would not have led to a change in treatment or the patient's survival because the patient was already receiving appropriate therapy for the missed condition, no effective treatment was available at that time, or there was not enough time to introduce effective treatment to change outcome. Class III included diseases that were related to the terminal process but not directly related to death, for which detection before death would not have changed treatment or outcome. Class IV included important diagnoses unrelated to the cause of death that eventually could have affected outcome if identified and treated. Class V was defined as absence of unexpected findings.

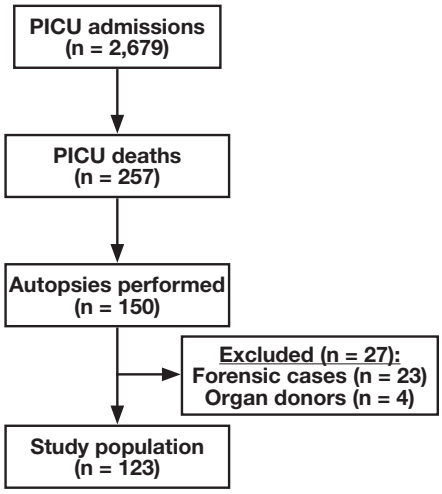

Figure 1 Flowchart of the study.

Statistical Analysis

Analysis was made using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Data were expressed as median (range) or number (%). Continuous variables were compared by the Mann-Whitney *U* test and categorical variables by the Fisher exact test. A *P* value less than .05 was considered statistically significant.

Results

From January 1, 2011, to December 31, 2015, a total of 2,679 children were admitted to the two PICUs of our university hospital, and 257 (9.6%) died. One hundred fifty (58.4%) patients underwent autopsy; 123 were included in the study. Forensic cases (deaths related to trauma, n = 17; submersion injury, n = 5; and foreign body aspiration, n = 1) and organ donors (n = 4) were excluded. The flow diagram of the study is shown in **Figure 1**.

Of the 123 patients included in the study, 68 (55.3%) were male and 55 (44.7%) were female. Patients' median age was 2.7 months (range, 0.07-184 months); 36 (29.3%) were neonates, 88 (71.5%) were younger than 1 year. Median length of PICU stay before death was 6 days (range, 0.02-330 days). Sixty-six (53.7%) were medical patients

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Table 1
Clinical Cause of Death

Cause of Death	No. (%)
Cardiogenic shock	28 (22.8)
Septic shock	26 (21.1)
Septic and cardiogenic shock	23 (18.7)
Respiratory failure	16 (13.0)
Intracranial hypertension	9 (7.3)
Hemorrhagic shock	8 (6.5)
Septic and hemorrhagic shock	5 (4.1)
Cardiogenic and hemorrhagic shock	4 (3.3)
Multiple-organ dysfunction syndrome	3 (2.4)
Cardiac arrest	1 (0.8)

and 57 (46.3%) were surgical patients; 46 (37.4%) had undergone cardiac surgery for congenital heart disease. Eighteen patients (14.6%) were previously healthy. The clinical cause of death is shown in **Table 1**.

Autopsy was not performed on 107 patients (41.6%); 51 (48.0%) were male and 56 (52.0%) were female. Patients' median age was 19 months (range, 0.06-216 months); seven (6.5%) were neonates and 44 (41.0%) were younger than 1 year. Their median length of PICU stay prior to death was 8 days (range, 0.05-170 days). Eighty-seven (81.3%) were medical patients and 20 (18.7%) were surgical patients. The most common clinical diagnoses of the primary underlying diseases at PICU admission were hematologic/oncologic disease (n = 28; 26.2%), postoperative cardiac surgery (n = 16; 15%), nonoperated congenital heart disease (n = 10; 9.3%), gastrointestinal/liver disease (n = 10; 9.3%), neurologic disorder (n = 9; 8.4%), congenital or acquired immunodeficiency (n = 6; 5.6%), and postoperative noncardiac surgery (n = 4; 3.7%). Ten patients (9.3%) were previously healthy. Comparison of characteristics of patients who underwent autopsy vs those who did not have autopsy performed is shown in **Table 2**.

According to modified classification by Goldman et al,[3,6] complete concordance between clinical diagnoses and postmortem findings (class V) was observed in 86 patients (69.9%). Twenty (16.3%) patients had a class I discrepancy; 17 (85.0%) were surgical patients, and 15 (75.0%) had undergone cardiac surgery. Class I discrepancies were related to technical failure in seven patients (patients 1, 2, 4, 8, 10, 11, and 12), hemorrhagic complication in four (patients 3, 5, 9, and 13), improper surgical procedure in three (patients 7, 14, and 20), diagnostic error in three (patients 16, 17, and 19), infection in two (patients 15 and 18), and air leak syndrome in one patient (patient 6) **Table 3**. Eight (6.5%) patients had a class II discrepancy; seven (87.5%) were medical patients. Class II discrepancies were related to infection in three patients (patients 21, 22, and 25), malignant neoplasm in two (patients 23 and 27), and congenital anomaly, hemorrhage, and autoimmune disease in one patient each (patients 24, 26, and 28, respectively) **Table 4**. Six (4.9%) patients had a class III discrepancy; three were surgical patients and three were medical patients. Class III discrepancies were necrotizing enterocolitis in two patients, pneumonia in two patients, chronic pyelonephritis in one patient, and pulmonary abscess in one patient. Three (2.4%) patients had a class IV discrepancy; all were medical patients. Class IV discrepancies were glycogen storage disease, relapsed hypothalamic hamartoma, and disseminated cytomegalovirus infection in one patient each **Table 5**. There was no significant difference between patients with a class I or class II discrepancy and those with no clinicopathologic discrepancy (class V) in age (median, 4.8 months [range, 0.07-153 months] vs 2.6 months [range, 0.07-184 months], respectively; $P = .43$) or length of PICU stay (median, 10 days [range, 0.1-97 days] vs 6 days [range, 0.02-330 days], respectively; $P = .22$). Comparing 2011 and 2015, the rate of major discrepancies (classes I and II) decreased from 31.6% to 15% **Figure 2**.

Discussion

In this study, we found a major clinicopathologic discrepancy rate of 22.8%. Unexpected autopsy findings could have altered outcomes if known before death in 16.3% of our patients. Accordingly, recent studies of adults who died in the intensive care unit showed that discrepant clinicopathologic findings still exist in the modern era. Reported major discrepancy rates (classes I and II) ranged from 7.8% to 23.5%.[2,3,7] A systematic review of studies that reported diagnostic errors confirmed by autopsy in the PICU, which included children who died in the 1990s and early 2000s, showed that major errors occurred in 20.2% of patients.[8] In children who died in the PICU from 2000 to 2005, the rate of major discrepancies between clinical and postmortem diagnoses was 8.6% to 26.4%.[4,5] Hence, our study corroborates previous data showing that autopsy continues to provide important and new information to clinicians who take care of complex critically ill patients. The most common class I and class II errors reported in critically ill children and neonates were related to missed infection and vascular events.[8,9] In contrast, almost half of our study population were surgical patients, and most class I errors revealed by autopsy were related to the surgical procedure. Interestingly, in postoperative cardiac surgery patients, autopsy revealed major unexpected findings in one-third (15/46). In 11 of 15 patients, class I discrepancies were related to the surgical procedure, including technical failure (n = 7), hemorrhagic complication (n = 1), and improper surgical procedure (n = 3), and in three patients, autopsy revealed diagnostic errors. Infection was the major

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Table 2
Comparison of Patients Who Underwent Autopsy With Those Who Did Not Have Autopsy Performed[a]

Characteristic	Autopsy (n = 123)	No Autopsy (n = 107)	*P* Value
Age, median (range), mo	2.7 (0.07-184)	19 (0.06-216)	<.0001
Male sex	68 (55.3)	51 (48.0)	.29
Length of PICU stay, median (range), d	6 (0.02-330)	8 (0.05-170)	.53
Primary specialty			
Medical	66 (53.7)	57 (46.3)	
Surgical	87 (81.3)	20 (18.7)	<.0001
Underlying primary disease at PICU admission			<.0001
Postoperative cardiac surgery	46 (37.4)	16 (15.0)	
Nonoperated congenital heart disease	17 (13.8)	10 (9.3)	
Postoperative noncardiac surgery	11 (8.9)	4 (3.7)	
Neurologic disorder	6 (4.9)	9 (8.4)	
Inborn errors of metabolism	6 (4.9)	2 (1.9)	
Gastrointestinal/liver disease	5 (4.1)	10 (9.3)	
Hematologic/oncologic disease	4 (3.3)	28 (26.2)	
Immunodeficiency	1 (0.8)	6 (5.6)	
Other	9 (7.3)	12 (11.2)	
None (previously healthy)	18 (14.6)	10 (9.3)	

PICU, pediatric intensive care unit.
[a]Data are expressed as number (%) unless otherwise indicated.

Table 3
Class I Discrepancies

Patient No.	Age, mo	Sex	Length of PICU Stay, d	Clinical Diagnoses	Autopsy Findings	Categories of Discrepancy
1	0.6	M	7	Postoperative tetralogy of Fallot, cardiogenic shock	Severe residual infundibular stenosis	Technical failure
2	1.3	M	17	Postoperative Damus-Kaye-Stansel surgery, cardiogenic shock	Closed atrial septal defect with a patent foramen ovale	Technical failure
3	0.07	F	2	Pulmonary atresia with intact ventricular septum, postoperative systemic-to-pulmonary artery shunt, hemorrhagic shock	Massive intraperitoneal bleeding	Hemorrhagic complication
4	0.13	F	1	Interrupted aortic arch and mitral valve hypoplasia, postoperative end-to-side anastomosis of the descending aorta to the ascending aorta, cardiogenic shock	Severe hypoplasia of the ascending aorta, left uncorrected	Technical failure
5	10	M	35	Severe acute respiratory distress syndrome, pulmonary hypertension, left-sided pneumothorax, septic shock	Massive hemopericardium with cardiac tamponade, right ventricle laceration by the chest tube	Hemorrhagic complication
6	1,9	M	13	Respiratory syncytial virus bronchiolitis, pneumonia, severe acute respiratory distress syndrome, pulmonary hypertension, respiratory failure	Pneumomediastinum, pneumopericardium, pneumothorax, pneumoperitoneum	Air leak syndrome
7	7	F	68	Postoperative Glenn surgery, deep venous thrombosis (right vena cava, right jugular vein), cardiogenic shock	Pulmonary arteriolar wall thickness suggestive of severely elevated pulmonary vascular resistance	Improper surgical procedure
8	0.2	M	1	Pulmonary atresia, tricuspid atresia, patent ductus arteriosus, postoperative systemic-to-pulmonary artery shunt (ductus arteriosus left open), cardiogenic shock	Thickening of the aortic ostium	Technical failure
9	3.6	M	2	Autosomal recessive polycystic kidney disease, gastric compression by the left kidney, postoperative left nephrectomy, disseminated intravascular coagulation, hemorrhagic shock	Hemorrhagic ascites with left retroperitoneal bleeding and adrenal hemorrhage	Hemorrhagic complication

(cont)

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Table 3 (cont)

Patient No.	Age, mo	Sex	Length of PICU Stay, d	Clinical Diagnoses	Autopsy Findings	Categories of Discrepancy
10	0.53	F	1	Unbalanced complete atrioventricular septal defect, transposition of great arteries, TAPVC—supracardiac type, postoperative TAPVC correction, cardiogenic shock	Anastomosis of the venous confluence to the left atrium compressed by the heart	Technical failure
11	2	M	55	Hypoplastic left heart syndrome, postoperative bilateral pulmonary artery banding, pneumonia, cardiogenic and septic shock	Very restrictive atrial septal defect	Technical failure
12	14	M	1	Situs inversus totalis, dextrocardia, pulmonary atresia, aorta connected to the right ventricle, atrial septal defect, ventricular septal defect, postoperative atrial septal defect closure, creation of a tunneling patch between the left ventricle and the aorta and right ventricle-to-pulmonary artery conduit placement, cardiogenic shock	Postrepair circulation was in parallel: right atrium connected to the right ventricle connected to the aorta and left atrium connected to the left ventricle connected to the pulmonary artery	Technical failure
13	6	F	3	Biliary atresia, late postoperative Kasai surgery, postoperative acute abdomen and enterocutaneous fistula repair, septic and hemorrhagic shock	Massive hemoperitoneum	Hemorrhagic complication
14	3.3	M	60	Ebstein anomaly with severe tricuspid insufficiency, mitral valve stenosis and hypoplastic left ventricle, postoperative tricuspid and mitral valve repair, necrotizing enterocolitis, residual severe tricuspid regurgitation, cardiogenic and septic shock	Large area of ischemia in the anterior wall of the left ventricle, moderate hypoplasia of the mitral valve, mild hypoplasia of the aortic arch	Improper surgical procedure
15	2.6	F	50	Pulmonary atresia with ventricular septal defect and patent ductus arteriosus, postoperative anastomosis between the right ventricle and the pulmonary artery bifurcation, acute respiratory failure due to upper airway obstruction	Severe cytomegalovirus pneumonia	Infection
16	1.8	M	42	Unbalanced complete atrioventricular septal defect with pulmonary atresia, postoperative systemic-to-pulmonary artery shunt, severe pulmonary hypertension, cardiogenic shock	Associated TAPVC—infracardiac type	Diagnostic error
17	0.6	M	15	Transposition of great arteries, ventricular septal defect, atrial septal defect, patent ductus arteriosus, supravalvar pulmonary stenosis, postoperative arterial switch operation with plasty of main pulmonary artery, cardiogenic and septic shock	Severe infundibular pulmonary stenosis	Diagnostic error
18	2	F	5	Acute gastroenteritis, hemophagocytic lymphohistiocytosis (primary?, secondary?), refractory septic shock	Disseminated invasive aspergillosis	Infection
19	62	F	7	Unbalanced complete atrioventricular septal defect, late postoperative bilateral Glenn surgery, cardiorespiratory arrest, refractory cardiogenic shock	Thrombosis of the right superior vena cava	Diagnostic error
20	7.3	M	97	Postoperative tetralogy of Fallot, cardiogenic and septic shock	Pulmonary arteriolar wall thickness suggestive of severely elevated pulmonary vascular resistance	Improper surgical procedure

PICU, pediatric intensive care unit; TAPVC, total anomalous pulmonary venous connection.

misdiagnosis in only one patient. Studies of postoperative cardiac surgery in adults showed major discrepancies between clinical and autopsy cause of death in 7% to 23.1% of patients.[10-12] Premortem unknown cardiac surgery–associated pathologic findings, including hemorrhage and technical failure, have been reported in 5% to 18.2% of

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Table 4
Class II Discrepancies

Patient No.	Age, mo	Sex	Length of PICU Stay, d	Clinical Diagnoses	Autopsy Findings	Categories of Discrepancy
21	41	M	81	Child abuse, meningitis, pneumonia, sepsis, severe intracranial hypertension, postoperative decompressive craniectomy, multiple-organ dysfunction syndrome	Septic embolus in coronary artery	Infection
22	142	M	27	Refractory status epilepticus, acute abdomen, septic shock	Acute pancreatitis, necrotizing enterocolitis	Infection
23	15	M	0.43	Hepatic failure, respiratory failure, lymphadenopathy and hepatosplenomegaly, septic and hemorrhagic shock	Diffuse large B-cell lymphoma	Malignant neoplasm
24	18	F	7	Bronchopneumonia with abscess formation, upper gastrointestinal bleeding, septic and hemorrhagic shock	Ectopic pancreatic tissue in the gastric wall	Congenital anomaly
25	6	M	15	Genetic syndrome, multiple ventricular septal defects with pulmonary hypertension, hydrocephalus with ventriculoperitoneal shunt, pneumonia, septic shock, respiratory failure	Suppurative meningitis	Infection
26	153	M	15	Acute myeloid leukemia (M3), disseminated intravascular coagulation, central nervous system bleeding, hemorrhagic shock	Massive hemoperitoneum	Hemorrhage
27	6	M	0.1	Respiratory syncytial virus infection, acute respiratory failure	Mediastinal neoplasm—malignant rhabdoid tumor	Malignant neoplasm
28	106	F	5	Myocarditis (viral?, systemic lupus erythematosus?), cardiogenic shock	Chronic myocarditis with extensive myocardial fibrosis	Inflammatory/autoimmune disease

PICU, pediatric intensive care unit.

adults.[10,11] A previous pediatric study showed that in 38% of children with congenital heart disease, autopsy revealed unsuspected cardiac abnormalities or surgical complications that could have altered management or outcome if known before death, and in 52% of patients who underwent surgery, death was related to surgical complications.[13] Moreover, the most prevalent cause of death in adolescents and adults with congenital heart disease was related to surgery in 33.3% of patients and to diagnostic errors in 3%.[14] A more recent pediatric study that investigated causes of death after surgery for congenital heart disease showed that 23% of deaths were related to residual anatomic defects, 8% to procedural complications, and 3% to diagnostic errors. In 16% of patients, a successful outcome could have been achieved by a different surgery strategy.[15] Therefore, our data corroborate previous results showing that technical issues and procedural complications are frequently related to death in patients who have cardiac surgery. Also, in accordance with previous studies,[14,15] we found that diagnostic errors continue to occur, despite advancement in imaging techniques.

We observed that over the study period, the rate of major errors decreased to less than half, which shows the importance of autopsy as an educational tool that may contribute to improvement of team performance.

The main limitation of this study is the potential for selection bias, since only 58.4% of patients who died over the study period underwent autopsy. Moreover, patients who did not have autopsy performed were mainly medical patients, and their underlying primary disease at PICU admission was predominantly hematologic/oncologic disease, while almost half of the patients who underwent autopsy were surgical patients, and more than one-third were postoperative cardiac surgery patients. These may have influenced our results. Nevertheless, the main reason for not performing an autopsy in our deceased patients was refusal from the family.

Conclusions

Major discrepancies between clinical diagnoses and postmortem findings still occur, despite progress in imaging techniques and treatment modalities. However, discussion of clinical and autopsy findings at monthly mortality conferences might lead to a greater understanding of the cause of death and contribute to prevent

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Table 5
Class III and Class IV Discrepancies

Patient No.	Age, mo	Sex	Length of PICU Stay, d	Clinical Diagnoses	Autopsy Findings	Primary Specialty
Class III						
29	28	F	4	Congenital cytomegalovirus infection, cytomegalovirus meningoencephalitis, intracranial hypertension, brain death	Unilateral chronic pyelonephritis	Medical
30	0.1	M	4	Hypoplastic left heart syndrome, cardiogenic shock (death in operating room)	Necrotizing enterocolitis	Surgical
31	12	F	1	Severe pulmonary artery stenosis, severe subvalvar aortic stenosis, atrial septal defect, acute suppurative otitis media, meningitis?, cardiogenic and septic shock	Lobar pneumonia	Medical
32	2.2	F	2	Spastic tetraparesis, pertussis, pneumonia, acute respiratory failure, septic shock	Necrotizing enterocolitis	Medical
33	144	F	10	Bacterial meningoencephalitis, cerebral abscess, postoperative drainage of cerebral abscess, cerebral venous thrombosis, brain death	Pulmonary abscess	Surgical
34	0.1	F	1	Hypoplastic left heart syndrome, postoperative pulmonary artery branches banding and atrioseptectomy, cardiogenic shock	Pneumonia	Surgical
Class IV						
35	0.2	F	0.7	Aspiration pneumonia, renal and hepatic malformation, acute respiratory distress syndrome, septic shock	Glycogen storage disease	Medical
36	116	M	1	Resected hypothalamic hamartoma, pneumonia, acute respiratory failure, refractory septic shock	Relapsed hypothalamic hamartoma	Medical
37	0.9	M	2	Incarcerated inguinal hernia (manually reduced), acute abdomen, acute kidney injury, septic shock, persistent thrombocytopenia since birth	Disseminated cytomegalovirus infection	Medical

PICU, pediatric intensive care unit.

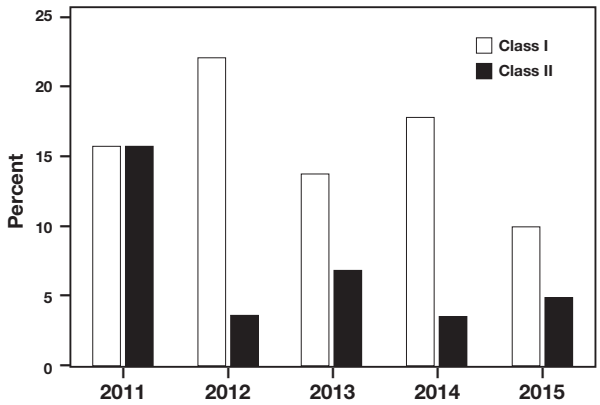

Figure 2 Class I and class II errors over the study period.

further errors, which may improve team performance and minimize unfavorable patient outcomes.[10,12] Our results emphasize the importance of autopsy to clarify the cause of death and its potential contribution to patient safety and quality of care.

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