
CLINICAL SCIENCE

**CLINICO-PATHOLOGICAL DISCREPANCIES IN A
GENERAL UNIVERSITY HOSPITAL IN SÃO PAULO,
BRAZIL**

Fabiana Kotovicz, Thais Mauad, Paulo H. N. Saldiva

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INTRODUCTION: The autopsy rate has continuously diminished over the past few decades, reducing the quality of medical care and the accuracy of statistical health data.

OBJECTIVE: To assess the accuracy of clinical diagnoses by comparing *pre-* and *postmortem* findings, and to identify potential risk factors for misdiagnoses.

METHODS: Retrospective evaluations performed between June 2001 and June 2003 in a 2500-bed tertiary university hospital in São Paulo, Brazil, including 288 patients who died at that institution and had a *postmortem* examination.

RESULTS: Clinical and autopsy records were reviewed and compared for categorization using the adapted Goldman criteria. The overall major and minor discrepancy rates were 16.3% and 28.1%, respectively. The most common missed diagnoses were pulmonary embolism, pneumonia, and myocardial infarction, and the most prevalent underlying diseases were infectious diseases, cerebro-cardiovascular conditions, and malignancies. Patients age 60 or older had an increased risk of diagnostic disagreement, as did female patients. The period of hospitalization, last admission unit at the hospital and underlying disease were not significantly related to the *pre-mortem* diagnostic accuracy.

DISCUSSION: The discrepancy rate found in this study is similar to those reported globally. The factors influencing diagnostic accuracy as well as the most commonly missed diagnoses are also consistent with the literature.

CONCLUSION: Autopsy remains a crucial tool for improving medical care, and effort must be focused on increasing its practice worldwide.

KEYWORDS: Autopsy; Accuracy; Comparison; Elderly; Female.

INTRODUCTION

The value of autopsy for detecting incorrect diagnoses and as an instrument for quality control of patient care has been confirmed by several studies since the beginning of the last century.¹⁻³ A considerable number of authors have presented the necroscopic exam as an important tool for research, medical education, quality control in clinical service, identification of new diseases or new manifestations of already known diseases,⁴ and evaluation

of the effectiveness of therapy strategies, as well as for establishing the cause of death.⁵⁻⁷

Despite overwhelming scientific evidence of the merits of the *postmortem* exam in modern medical practice, autopsy rates have fallen over the last few decades.⁸⁻¹⁰ Autopsy was conducted on an average of 50% of deaths in the 1940s, but less than 10% in the 1990s, and these statistics apply both at university and community hospitals, and both in developed and in most developing countries.¹¹⁻¹³

The decreasing numbers of autopsies have had many repercussions on systematic errors and bias in research data. Death certificates need to be accurate, as the data they provide are the basis of epidemiology and health statistics. Meanwhile, since the main diagnoses and causes of death are, in most cases, established without autopsy records, many decisions regarding public health are made based on incorrect or incomplete information.

Laboratory of Air Pollution, Department of Pathology, Faculdade de Medicina da Universidade de São Paulo – São Paulo/SP, Brazil.

Phone: 55 11 3061.7173

Email: tmaud@usp.br

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The number of studies exploring the ability of autopsy to clarify medical cases has increased in the last two decades as part of an effort to increase the number of autopsies worldwide. Most studies focus on particular situations, such as patients from specific units at the hospital (e.g., ICU), age ranges (e.g., pediatrics), or underlying diseases (e.g., hematological or neoplastic).^{14,15} In a general hospital, the study of clinico-autopsy discrepancies is important as an internal check on the quality of care. It may identify selected disease groups, patients, or medical units with a higher risk for discrepancies.

Therefore, the present study sought to delineate the importance of autopsy from a general, large, 2500-bed university hospital in Brazil by determining the clinico-pathological discrepancies in patients categorized into different groups according to their specific characteristics (age, sex, underlying disease, duration of hospitalization, admission unit). For this purpose, the Goldman discrepancy classification⁵ was used as a basis of comparison between clinical and autopsy diagnoses, and as a method of classifying the discrepancies.

METHODS

This study was approved by the Ethics Committee of the University of São Paulo Medical School.

This was a retrospective cross-sectional study performed by comparing the diagnoses listed on clinical and autopsy reports of 288 patients who were admitted and who died at the Hospital das Clínicas, São Paulo University Medical School between June 2001 and June 2003. This institution provides tertiary medical care for any medical specialty.

There were 3,512 deaths in the period of the study, with 2,529 (72%) patients submitted to teaching autopsies. The eligibility criteria was death after being admitted as an inpatient at the aforementioned institution for any reason excluding stillbirths, prematurity, and congenital malformations.

One internist and a senior pathologist analyzed clinical history and autopsy reports of nonconsecutive, randomly chosen patients. *Pre-* and *postmortem* diagnoses were classified into four distinct classes according to the level of agreement, adapted from the Goldman criteria: Class I: Major missed diagnoses that certainly would have led to a change in management with increased chances for survival or cure, such as unrecognized treatable infection; Class II: Major missed diagnoses that could have led to a change in management increasing survival or leading to cure, such as missed pulmonary embolism in a patient with disseminated malignant neoplasm; Class III: Missed minor diagnoses not directly related to the cause of death; Class IV: absolute agreement. As in other studies,^{14,16,17} only a single category

of discrepancy was assigned to each patient according to the worst type of disagreement. Therefore, if a patient had two major missed diagnoses, one classified as class I and another as class II, only class I was considered. For the purpose of analysis, classes I and II were grouped as discordance, and classes III and IV were labeled as concordance. If there was a disagreement in the categories, the medical and autopsy records were reviewed by another senior pathologist, and a consensus was reached after discussion.

From each patient, data were identified by age, gender, length of hospitalization, admission unit, medical history, and major and minor diagnoses from clinical and autopsy reports. Analysis of concordance vs. discordance was based on an evaluation of the medical history, laboratory and radiological exams, the patient's course of disease, the physician's final clinical diagnoses, and the macroscopic and microscopic findings of the autopsy. Incomplete medical records were excluded from the analysis.

The duration of hospitalization was classified as either less than 24 hours, two to seven days, or more than seven days. The patient's age was categorized as either younger than 60 or 60 years old or older. Admission units were categorized as intensive care, medical/surgical wards, and emergency room. The basic causes of death were grouped into four categories: cerebro-cardiovascular, malignancies, infectious, and others.

The necessary sample size for this study was estimated using statistically validated equations for this purpose, taking the following parameters: 5% acceptable margin of error; 95% confidence level; estimated population size for the studied period equal to 2500; and response distribution of approximately 25% for discordant cases (based on similar previous studies). The estimated minimum sample size, according to the chosen parameters, was 259.

The SPSS program version 13.0 was used to calculate descriptive data and the influence of the following variables on the diagnostic accuracy: age, sex, duration of hospitalization, admission unit at the hospital, and category of underlying disease presented. A univariate analysis using Pearson's chi-square test investigated the relationship between having a discordant (class I or II) diagnosis versus concordant (class III or IV) diagnosis and all other variables studied. The relationship between the independent variables was also tested.

The alpha level for the threshold of statistical significance was 0.05. All potential explanatory variables were assessed for collinearity (nonindependence). After identifying all the possible related variables with a concordant or discordant diagnosis after necropsy ($p < 0.05$), a multiple logistic regression was developed to exclude confounding variables, to confirm statistical significance, and to determine both

the odds ratio and the 95% confidence interval. All the assumptions of both tests were met.

RESULTS

The following data were collected between June 2001 and June 2003. From a total of 312 patients, 24 were excluded from this study because they had incomplete medical charts.

Of the 288 patients undergoing autopsy who were analyzed, 158 were males and 130 were females. Patients' ages ranged from 0 to 94 years, their median ages were 54 for both men and women and their IQRs were 42-70 for men and 37-71 for women. A total of 122 (58%) patients were 60 years old or older. Table 1 summarizes the diagnostic categories of the patients.

The median length of stay at the hospital prior to death was nine days with an IQR of 3-20 days, ranging from one to 204 days. Thirty (10%) patients died within 24 hours of admission, 97 (34%) patients died between two and seven days, and 161 (56%) patients died more than seven days after admission to the hospital. In terms of the hospital unit in which the patients died, 111 (39%) patients were admitted to the emergency room at the time of death, 112 (39%) were admitted to the intensive care unit, and 65 (23%) were admitted to the wards.

The patients' major underlying diseases were: 70 (24%) infectious disease, 57 (20%) cerebro-cardiovascular disease, 55 (19%) malignancies, and 106 (37%) other diseases including gastrointestinal, rheumatologic, and hematological diseases. In 241 (84%) of the cases, the diagnoses were concordant (class III and IV findings), and there were major discrepancies (class I or II findings) in 47 (16%) of the cases. The discordant diagnoses are shown in Table 2.

Disagreements between clinical and pathological diagnoses occurred in 19 (6.6%) patients younger than 60 years of age and in 28 (9.7%) patients aged 60 or older. The chance of having a discrepant diagnosis after dying was significantly different for both age ranges (p= 0.009). The rate of diagnostic discordance was 10% (29 cases) for women and 6.2% (18 cases) for men. The correlation between sex and diagnostic disagreement was also statistically significant (p= 0.013).

We also studied the effect of length of hospitalization on the incidence of discrepancies. Disagreement between clinical and pathological diagnosis was found in three (1.0%) of the patients who stayed 24 hours or less at the hospital, in 16 (5.6%) of the patients who had two to seven days of hospitalization, and in 28 (9.7%) of the patients who were hospitalized for more than seven days. There appears to be no relationship between these variables (p= 0.602).

Table 1 - Concordant and discordant cases according to clinical characteristics

	Concordant Cases No. (%) N =241	Discordant Cases No. (%) N = 47	P value*	Odds ratio (CI-95%)
Sex			0.013	2.28 (1.19-4.37)
Male	140 (58)	18 (38)		
Female	101 (42)	29 (62)		
Age			0.009	2.35 (1.23 - 4.85)
< 60 y	147 (61)	19 (40)		
≥ 60 y	94 (39)	28 (60)		
Hospital length of stay			0.602	
≤ 24 h	27 (11)	3 (6)		
2 to 7 days	81 (34)	16 (34)		
More than 7 days	133 (55)	28 (60)		
Underlying disease			0.241	
Cardiovascular	47 (20)	10 (21)		
Malignancy	46 (19)	9 (19)		
Infectious	54 (22)	16 (34)		
Others	94 (39)	12 (26)		
Last Admission Unit			0.126	
Wards	55 (23)	10 (21)		
Emergency room	87 (36)	24 (51)		
Intensive care unit	99 (41)	13 (28)		

* P value refers to univariate analysis.

Table 2 - Details of discordant cases

<i>Clinical Diagnoses</i>	<i>Autopsy Diagnoses</i>
Class I discordance	
1) Hypertension, stroke	1) Myocardial infarction
2) Hypertension, congestive heart failure, pneumonia	2) Pneumonia, pulmonary embolism
3) Renal failure, metabolic encephalopathy	3) Renal failure, myocardial infarction
4) Diabetes, pneumonia	4) Diabetes, myocardial infarction
5) Pneumonia, sepsis	5) Pneumonia, myocardial infarction
6) Pneumonia, sepsis	6) Pneumonia, myocardial infarction
7) AIDS**, hepatitis B	7) AIDS, hepatitis B, pneumonia
8) AIDS, pneumocystosis, pneumonia, septic shock	8) AIDS, pneumocystosis, tuberculosis, hepatitis B
9) AIDS, peritonitis, pneumonia	9) AIDS, pneumonia, tuberculosis
10) AIDS, pneumocystosis, pneumonia	10) AIDS, tuberculosis
11) Hypertension, congestive heart failure	11) Hypertension, meningitis
12) Cirrhosis, hepatic encephalopathy	12) Cirrhosis, gastrointestinal hemorrhage
13) Cirrhosis, renal failure, sepsis	13) Cirrhosis, gastrointestinal hemorrhage
14) Lymphoma, cholecystopathy	14) Lymphoma, infectious peritonitis, pneumonia
15) Sickle cell disease	15) Sickle cell disease, pulmonary embolism
16) Hepatitis C, systemic lupus erythematosus, pneumonia, sepsis	16) Hepatitis C, systemic lupus erythematosus, pulmonary embolism
17) Systemic lupus erythematosus, renal failure	17) Systemic lupus erythematosus, pyelonephritis, pneumonia
18) Hypertension, diabetes, Congestive heart failure, septic shock	18) Hypertension, diabetes, gastrointestinal hemorrhage, peptic ulcer
19) Cirrhosis, hepatorenal syndrome	19) Cirrhosis, pneumocystosis
20) Colon cancer	20) Colon cancer, perforated colon, infectious peritonitis
21) Lymphoma, pneumonia	21) Lymphoma, pulmonary embolism
22) Pancytopenia, pneumonia	22) Leukemia, pneumonia, intracranial hemorrhage, cirrhosis
23) Bone marrow aplasia, osteomyelitis, renal failure	23) Gastrointestinal hemorrhage, bone marrow aplasia, osteomyelitis
24) Diabetes, intracranial hemorrhage, renal failure	24) Diabetes, intracranial hemorrhage, pulmonary embolism
25) Hepatocarcinoma, septic shock	25) Hepatocarcinoma, erysipelas, pneumonia, pulmonary embolism
26) Hypertension, sepsis	26) Hypertension, cerebral infarction
27) AIDS, hematological cancer, pneumonia	27) AIDS, tuberculosis, hematological cancer
28) Wilson's disease, acute respiratory distress syndrome, renal failure	28) Wilson's disease, cirrhosis, intracranial hemorrhage
Class II discordance	
1) Congestive heart failure, cardiogenic shock, pulmonary edema	1) Mitral and aortic valvulopathy, pneumonia, respiratory insufficiency
2) Diabetes, hypertension, congestive heart failure	2) Diabetes, hypertension, myocardial infarction
3) Ischemic lower limb with amputation, sepsis	3) Ischemic lower limb with amputation, pneumonia
4) Aortic aneurism, sepsis	4) Aortic aneurysm, pneumonia
5) Uterine cancer, venous thrombosis, cerebral infarction	5) Uterine cancer, venous thrombosis, pulmonary embolism, cerebral infarction
6) Hepatitis C, tuberculosis, sepsis	6) Pulmonary cancer, hepatitis C, cirrhosis
7) Hepatocarcinoma, upper gastrointestinal bleeding	7) Hepatocarcinoma, intracranial hemorrhage, upper gastrointestinal bleeding
8) Pneumonia, pulmonary embolism	8) Metastatic pulmonary cancer with unknown primary site
9) Pneumonia	9) Pulmonary carcinoma, pneumonia
10) Thyroid carcinoma, pneumonia, septic shock	10) Metastatic pulmonary cancer, thyroid carcinoma, pneumonia
11) Intracranial metastasis with unknown first site cancer, pneumonia	11) Prostate cancer, disseminated metastasis, pneumonia
12) Endocarditis, septic shock, meningitis	12) Endocarditis, meningitis, pulmonary embolism
13) Neurocysticercosis, ventriculitis	13) Neurocysticercosis, ventriculitis, pulmonary embolism
14) AIDS, neutropenic fever, sepsis	14) AIDS, pneumonia
15) AIDS, pneumonia	15) AIDS, pneumonia, tuberculosis
16) Obstructive lung disease	16) Obstructive lung disease, pneumonia
17) Discitis, renal failure	17) Discitis, osteomyelitis, pneumonia
18) Tuberculosis, pulmonary cancer	18) Intracranial hemorrhage, pulmonary embolism, tuberculosis, pulmonary cancer
19) Ovarian cancer with metastasis	19) Ovarian cancer with metastasis, pneumonia

* Each number refers to one studied patient. **Acquired Immunodeficiency Syndrome

Similarly, the last admission unit at the hospital did not influence the probability of misdiagnosis ($p=0.126$), and the distribution of diagnostic disagreement was as follows: 10 (3.5%) of the patients in the wards, 24 (8.3%) of the patients in the emergency room, and 13 (4.5%) of the patients in the ICU. Regarding the underlying disease, class I or II findings occurred in 10 (3.5%) of the patients with cardiovascular disease, nine (3.1%) of the patients with malignancies, and in 16 (5.5%) of the patients with infectious disease. The p value was 0.241.

A logistic regression was performed to study the two possibly correlated variables (age and sex), which in both cases continued to confirm the alternative hypothesis. Therefore, female patients had a significantly greater risk of having a discordant diagnosis in comparison to male patients (OR: 2.28; CI-95%: 1.19 - 4.37), and patients who were 60 years old or older had 2.35 times the chance of a discordant diagnosis (CI-95%: 1.23 - 4.85) in patients younger than 60 years old.

DISCUSSION

In this study, we analyzed clinico-pathological discrepancies in a large general academic hospital with a high autopsy rate in São Paulo, Brazil. Our data show that the overall major discrepancy rate was 16.3% (9.7% class I and 6.6% class II). The rate of cases presenting only minor discrepancies, classified as class III, was 28.1%. These results are comparable to most studies in general hospitals, which present major discrepancy rates varying from 11% to 48%.^{18,19} Despite technological improvements in medicine, a significant number of authors have stressed the fact that these rates have remained essentially unchanged in the last decades, although the nature of the diagnostic error varies continuously.²⁰⁻²² Coradazzi et al.⁹ compared two periods (1972-1985 and 1992-1996) in a Brazilian university hospital, and they reported 27.1% and 20.6% rates of disagreement, respectively.

In studies focusing on specific or more severe clinical situations, we found similar or higher ranges. Avgerinos-Bjornsson²³ reported a rate of 17% of missed diagnoses in patients presenting malignancies, and Burton et al.²⁴ found 44%. In a study by Bonds et al.,¹¹ 43.1% of all patients with an infectious disease that was known before death had another infectious condition that was unknown until the time of the autopsy. Most of the studies exploring ICU discrepancy rates found higher numbers, as follows: 19.8% in Singapore,¹⁵ 21% in Belgium,¹⁶ 33.3% in Brazil,⁷ 31.7% in France,²⁵ and 39% in the United Kingdom.²⁶

In our study, infectious diseases were found to be the main underlying cause of death (24%), followed by cerebro-cardiovascular conditions (20%), and malignancies (19%).

A study by Juriae et al.¹⁸ in a general hospital in Croatia noted the causes of death to be 40.9% cardiovascular conditions (mostly myocardial infarction and pulmonary embolism), 25.2% malignancies (mostly leukemia and lymphoma), and 12.9% infectious diseases (mostly pneumonia, peritonitis, and tuberculosis). In Chile, Chacón et al.¹² found a predominance of cardiovascular conditions (29.8%), malignancies (26.3%), and gastrointestinal diseases (21%). The high prevalence of infectious diseases in our study can be explained by the fact that Brazil possesses many contributing factors for parasitic diseases, such as low socioeconomic status, malnutrition, and deficiency in primary health care. Cerebro-cardiovascular diseases and malignancies are increasingly common causes of death all over the world, mostly due to lifestyle changes. Sarode et al.²⁷, in India, a country similar to Brazil in many ways, found a distribution of 46.8% for infectious diseases, 17.1% for cardiovascular diseases, and 14.3% for malignancies. Only one study¹⁹ reports a significant association between the frequency of discordant cases and the underlying disease, wherein the respiratory system exhibited the highest discrepancy rate.

Pulmonary embolism accounted for the majority of class I or II misdiagnosed conditions in various studies,^{14,22} including this one. We had nine patients with a massive pulmonary embolism that was not suspected clinically. Pneumonia was the second most frequent missed diagnosis, present in eight patients, and myocardial infarction was the third, occurring in six patients. Ischemic or hemorrhagic intracranial vascular disease was not clinically recognized in four patients, and four patients had received treatment for presumed pneumonia or pneumocystosis when they actually had tuberculosis. Malignancies were not found before death in four cases. Three patients presenting disseminated neoplasm were thought to have tuberculosis, localized thyroid carcinoma, and pneumonia, respectively. The fourth had a clinically known intracranial metastasis, and prostate cancer was only established as the primary site *postmortem*. Missed gastrointestinal hemorrhage was seen in four patients, and one patient died from a missed perforation in a previously diagnosed colon neoplasm. These data agree with the literature,^{18,19,22} which revealed that 50 to 67% of bronchopneumonias are not clinically anticipated, along with 34 to 40% of neoplasias, 23 to 84% of coronary disease, and 68 to 93% of pulmonary embolisms.

Several authors have emphasized that infectious diseases comprise the majority of missed causes of death in the latest studies, especially when reporting cases from the ICU setting.^{16,17} This is understandable because of the increasing exposure of our patients to broad-spectrum antimicrobials. These measures ultimately promote the emergence of more virulent

and resistant infections, such as nosocomial pneumonia, which are sometimes difficult to diagnose in terminal patients.

It might be expected that the longer a patient stays at the hospital, the more likely the clinical and autopsy diagnoses would be to agree. However, this is not consistent with our findings. As in most of other previous investigations of hospital-wide populations,^{14,21} we found no statistically significant correlation between the overall duration of hospitalization and the discrepancy rate. Gibson et al.¹⁹ and Spiliopoulou et al.¹⁰ compared patients who were hospitalized up to 24 hours with those hospitalized for more than one day. None of these studies found any significant results. However, Mort and Yeston¹⁷ and Maris et al.,¹⁶ found that lengths of stay longer than 2 and 10 days, respectively, were more likely to contribute to the occurrence of major errors discovered *postmortem*. Battle and colleagues²⁸ have suggested that diagnostic accuracy may decrease with increasing hospital time due to the failure of doctors to recognize new problems in patients who are already being treated for other diseases.

We did not find a statistically significant correlation between the last admission unit and the level of agreement, but such a correlation was noted in two previous studies. Gibson et al.¹⁹ found the lowest frequency of concordant diagnoses in the emergency room (33.6%) and the highest (68.4%) in the child health unit. In a study of hematological patients, Xavier et al.²⁹ reported that being admitted to a specialized hematological unit was associated with a significantly lower occurrence of misdiagnoses.

Discrepancy rates rose with advancing patient age. Patients 60 years old or older had 2.35 the chance of having a discrepant diagnosis in younger patients. These results are supported by several authors such as Spiliopoulou et al.¹⁰ and by Gibson et al.,¹⁹ who also found a lower diagnostic concordance among the elderly. These patients usually present multiple comorbidities and an unclear clinical presentation. Likewise, in cases with a poor prognosis, which are more common at this age, it is possible that the physician and the patient's family decide not to proceed with clinical investigations, which also can contribute to a greater chance of misdiagnosis in the older population.⁸ In addition, while advances in medical therapies have prolonged life expectancies, new diseases and new complications have emerged, especially opportunistic infections.²⁶

The chance of disagreement between clinico-pathological diagnoses was higher in women than in men by a factor of 2.28, but to our knowledge, very little is known about this finding. Only the studies by Battle et al.²⁸ (including 32 US hospitals) and by Avgerinos et al.²³ (from the Mayo Clinic) showed a greater frequency of major diagnostic discrepancies among females. A large number of previous studies found no correlation with sex,^{10,20} and one author¹⁹ found that males

had a significantly lower diagnostic concordance. The reasons for these findings are not clear.

LIMITATIONS

There are some limitations to this study, such as the small number of cases in proportion to the number of autopsies performed at the hospital in the study period and the fact that nonconsecutive cases were chosen. This is a retrospective study, and thus could have been imprecise in data collection. Furthermore, a selection bias may have also occurred since deaths that motivate a request for autopsy tend to be more challenging cases than the average. However, this argument is questionable considering the studies done by Cameron and colleagues³⁰ and by Landefeld et al.⁵ Their studies showed that the ability of doctors to detect which cases are more prone to result in undiscovered diagnoses usually fails. The high autopsy rate in this hospital during the study period (72%) potentially diminishes the selectivity factors. It is relevant to emphasize that the disclosed findings only apply to general university hospitals.

CONCLUSION

We conclude that the rates of disagreement between clinicians and pathologists' diagnoses concerning the cause of death are still high in both developed and developing countries, despite epidemiological differences and available technological resources. Since our study shows that events such as pulmonary embolism, myocardial infarction, and infectious diseases, especially pneumonia, remain very prevalent and often unrecognized conditions, it is important to highlight the need for maintaining a high level of suspicion for these diagnoses. Data on major discrepancies in pathological diagnoses in our institution can guide further research on diagnostic management.

This article aims to reinforce the importance of a minimum mandatory autopsy rate, as well as to increase the rate of mutual consultation between specialties through, for example, death conferences. This recommendation is corroborated by a prospective 5-year study³⁰ where diagnoses from necropsy and clinical reports were systematically discussed among clinicians and pathologists, resulting in a statistically significant improvement of diagnostic accuracy in the fifth year.

Autopsy still plays a relevant role in clinical practice, improving the quality of medical care. Therefore, difficulties in obtaining family authorization or scarce financial resources should not block attempts to increase autopsy rates.

The authors declare that they have no competing interests.

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