A Study of Consecutive Autopsies in a Medical ICU*

A Comparison of Clinical Cause of Death and Autopsy Diagnosis

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**Objective:** To determine the degree of concordance between clinical cause of death and autopsy diagnosis in a medical ICU (MICU) setting.

**Design:** Retrospective medical chart and autopsy report review.

**Setting:** MICU in a tertiary referral hospital.

**Patients:** Consecutive admissions to an MICU over a 2-year period from January 1, 1994, to December 31, 1995.

**Interventions:** None.

**Measurements and main results:** One thousand eight hundred patients were admitted to the MICU during the study period. There were 401 in-ICU deaths (22.3%). The autopsy rate was 22.7% (91 of 401). The mean ± SD age of the autopsied patients (55.1 ± 13.5 years) was lower than those without autopsy (62.4 ± 15.2 years; p < 0.001). The two groups were otherwise similar with regard to sex, race, APACHE (acute physiology and chronic health evaluation) III scores, and lengths of stay in the MICU and hospital. The discordance between clinical and postmortem diagnoses was 19.8% (95% confidence interval, 12 to 29%). There were no differences in age, sex, APACHE III scores, predicted mortality, and lengths of stay in MICU hospital between patients with concordant and discordant diagnoses. In 44.4% (8 of 18) of the discordant cases, management would have been modified had the autopsied diagnosis been made premortem. Seven of the autopsied patients had organ transplantation. Three of the patients who had organ transplantation had discordant diagnoses, including two patients with disseminated fungal infection that was not diagnosed clinically. Although the observed discordance in transplant patients (43%) was higher than in those without transplant (19%), the difference was not statistically significant (p = 0.15).

**Conclusion:** Younger patients tended to have a higher autopsy rate than older patients. The discordance between the clinical cause of death and postmortem diagnosis was 19.8%. In 44.4% of the discordant cases, knowledge of the correct diagnosis would have altered therapy.

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**Key words:** autopsy diagnosis; cause of death; clinical diagnosis; concordance; disseminated fungal infection; intensive care; organ transplantation; pulmonary embolism

**Abbreviations:** APACHE = acute physiology and chronic health evaluation; MICU = medical ICU; PE = pulmonary embolism; SICU = surgical ICU

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Autopsy rates have been declining worldwide.1–6 In US hospitals, the autopsy rates have fallen progressively from about 50% in the 1940s, to between 10% and 15% in 1985.5 The reasons for the decline in autopsy rates are as follows: economic (autopsy is costly and not reimbursable), legal (fear of litigation), attitudinal change (“time-consuming chore”), and exclusion of minimum mandatory au-
Autopsy rates as one of the accreditation criteria for US hospitals. There is also the tendency to believe that advances in medical technology provide greater diagnostic accuracy, which makes autopsy unnecessary. Autopsy remains one of the most reliable methods to validate clinical diagnoses. Various workers have investigated the frequency of premortem to postmortem diagnostic discrepancies in hospitalized patients that ranged from 6% to 60%. However, there are only few such studies in adult ICUs and one in the pediatric ICU. A study in a medical ICU (MICU) with an autopsy rate of 31% (41 of 132), reported that the clinical and pathologic cause of death differed in 34% (14 of 41), and postmortem findings would have changed clinical management in 27% (11 of 41) of the cases. Other studies in a surgical ICU (SICU) and multidisciplinary adult ICU reported similar rates of discrepancy between premortem clinical diagnoses and postmortem findings.

We therefore retrospectively analyzed consecutive autopsies over a 2-year period in an MICU in a tertiary-care hospital with state-of-the-art diagnostic facilities in order (1) to assess the accuracy of clinical diagnosis as compared to postmortem findings, and (2) to assess whether premortem knowledge of the autopsy findings would have altered patient management.

**MATERIALS AND METHODS**

**Study Patients**

Consecutive patients admitted to the MICU at the Cleveland Clinic Foundation over a 2-year period from January 1, 1994, to December 31, 1995, were studied retrospectively. The MICU is staffed by Residents from the Internal Medicine Residency Program, Fellows from the Pulmonary and Critical Care Department, and Attendings for the Pulmonary Department, board certified in internal medicine, pulmonary medicine, and critical care medicine. The medical staff makes rounds every day, and every medical decision is supervised and approved by the Attending. Consent for autopsy was routinely requested by the house-staff from the relatives of the deceased. In the autopsied population, the clinical cause of death as recorded in the medical charts was compared with the autopsy findings to assess the accuracy of clinical diagnosis. The charts of the autopsied patients were also reviewed in detail to determine whether the patient was terminally ill and not a candidate for resuscitation.

**Medical Records Review Process**

A research nurse extracted the following information from a computerized database system: age, sex, race, APACHE (acute physiology and chronic health evaluation) III score, and lengths of MICU and hospital stay. The clinical cause of death and the autopsy diagnosis were obtained from chart reviews and autopsy reports, respectively, by two of the authors (either D.Y.H.T., H.E., or S.T.). If there was still disagreement between the reviewers about the presence of a diagnostic error, two experienced critical care physicians (A.C.A. and H.P.W.) were consulted for an independent review.

**Review Criteria**

Both the clinical cause of death and autopsy findings were classified according to the International Classification of Diseases Ninth Revision. The clinical cause of death included the immediate cause of death and the underlying primary disease. Secondary diagnoses that were related to the primary diagnoses, or other antecedent conditions, which might have impacted on the patient’s prognosis and management, were included. Autopsy diagnoses included histologic and microbiological findings as listed in the final autopsy reports.

The diagnostic errors were classified in two categories. Class 1 errors were major misdiagnoses with direct impact on therapy. Class 2 diagnostic errors comprised major unexpected findings that probably would not have changed therapy for any of the following reasons: the patient was already receiving appropriate therapy, even though the diagnosis was not known; effective therapy was not available (eg, disseminated malignancy); the patient had presented with an acute cardiopulmonary arrest that was managed appropriately; or the patient had refused further investigations or treatment. Minor incidental findings, such as renal calculi and uterine fibroid, which were not related to the main diagnoses and did not contribute to the immediate cause of death, were omitted. All the clinical details were carefully considered in classifying clinical accuracy.

**Statistical Analysis**

Patients who had an autopsy and those who did not were compared with a t test or Wilcoxon rank-sum test for continuous variables and by the χ² test or Fisher’s Exact Test for categorical variables. Similar methods were used to assess association between concordance and various baseline and outcome factors. All tests were two sided, and a significance level of 0.05 was used for each hypothesis. All statistical analysis was performed using a software package (SAS version 6.12; SAS Institute; Cary, NC).

**RESULTS**

During the study period, there were 1,800 admissions to the MICU. The in-ICU mortality was 22.3% (401 of 1,800 patients). The autopsy rate was 22.7% (91 of 401 deaths). The patients who had an autopsy were younger than those without autopsy (p < 0.001; Table 1). There were no significant differences in sex, race, APACHE III scores, and lengths of stay in the MICU and hospital between these two groups (Table 1).

**Diagnosis Errors**

The discordance between clinical and postmortem diagnoses was 19.8% (18 of 91; 95% confidence interval, 12 to 29%). No significant association was found between discordant diagnosis and age, sex, race, APACHE III scores, or lengths of stay in MICU and hospital (Table 2). With 18 discordant
and 73 concordant diagnoses, we had about 80% power at the 0.05 significance level to detect absolute differences as small as 0.28 to 0.36 in the proportion with a certain characteristic between the two groups, and effect sizes (difference in means divided by standard deviation) of ≥ 0.75.

Among the 18 discordant cases, class 1 diagnostic errors were identified in 8 patients and class 2 errors in 10 patients. The details of the discordant cases are summarized in Tables 3, 4. All the misdiagnoses were confirmed by gross and microscopic examination, or by microbiological culture during postmortem study.

Three of the 18 discordant cases had organ transplantation (patients 1, 12, and 13), and 2 of them had disseminated fungal infections that were not diagnosed premortem (patients 12 and 13). However, both were empirically treated with the appropriate antifungal agents despite negative fungal cultures. The observed discordance in transplant patients (43%) was higher than in nontransplant patients (19%), but the difference was not statistically significant (p = 0.15).

Five of 24 patients (21%) with malignant disease (patients 7, 9, 10, 11, and 14) had inaccurate diagnoses. Two patients presented with disseminated malignancy (patients 9 and 11), and the primary sites were only established at postmortem. No association was found between discordant diagnosis and malignancy (p = 0.99).

**Discussion**

The 22.7% autopsy rate in our study is higher than the overall national hospital autopsy rates in the United States (12%) and some studies in the United

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### Table 1—Comparison of Autopsied and Nonautopsied Patients*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Autopsy Population, n = 91</th>
<th>Nonautopsy Population, n = 310</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55.1 ± 13.5</td>
<td>62.4 ± 15.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender, No. (%)</td>
<td>53 (58.2)</td>
<td>159 (51.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66 (72.5)</td>
<td>220 (71.6)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>23 (25.3)</td>
<td>80 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.2)</td>
<td>8 (2.6)</td>
<td></td>
</tr>
<tr>
<td>APACHE III†</td>
<td>107.4 ± 36.8</td>
<td>108.4 ± 35.6</td>
<td>0.82</td>
</tr>
<tr>
<td>MICU lengths of stay, d</td>
<td>5 (2, 12)</td>
<td>5 (2, 13)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hospital lengths of stay, d</td>
<td>9 (3, 17)</td>
<td>10 (4, 21)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or median (quartiles) unless otherwise indicated.
†APACHE III scores were not available for patients who died within 4 h, and lodgers in other ICUs (concordant cases, n = 85; discordant cases, n = 301).
§x² test.
¶t test.
||Wilcoxon rank-sum test.

### Table 2—Comparison of Concordant and Discordant Cases*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Concordant Cases, n = 73</th>
<th>Discordant Cases, n = 18</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>53.9 ± 12.8</td>
<td>60.1 ± 15.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Male gender, No. (%)</td>
<td>43 (58.9)</td>
<td>10 (55.6)</td>
<td>0.50</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>53 (72.6)</td>
<td>13 (72.2)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>18 (24.7)</td>
<td>5 (27.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Others</td>
<td>2 (2.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>APACHE III†</td>
<td>108.9 ± 36.8</td>
<td>101.2 ± 36.9</td>
<td>0.44</td>
</tr>
<tr>
<td>MICU lengths of stay, d</td>
<td>5 (2, 13)</td>
<td>3 (2, 7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hospital lengths of stay, d</td>
<td>10 (3, 19)</td>
<td>5 (3, 12)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or median (quartiles) unless otherwise indicated.
†APACHE III scores were not available for patients who died within 4 h, and lodgers in other ICUs (concordant cases, n = 68; discordant cases, n = 301).
|x² test.
|t test.
||Wilcoxon rank-sum test.
Kingdom (11 to 24%), and are comparable to the autopsy rates in two postmortem studies in adult ICUs (31% and 29%, respectively). The largest comparison of clinical and autopsy diagnoses was made by Britton, from 1970 to 1971. In his analysis of 400 consecutive deaths in the medical department with an autopsy rate of 96%, the main cause of death was erroneous in 30%. Our discordance between clinical and postmortem diagnosis was 19.8% (confidence interval, 12 to 29%).

Our observation that the mean age of the autopsied population was lower than nonautopsied patients was consistent with other studies. Campion et al, in their prospective study of 1,080 consecutive deaths among patients admitted to a MICU/coronary care unit, reported a significant drop in autopsy rate from 60% for those aged 16 to 34 years, to 23% for those aged ≥ 85 years. This is not surprising, as the motivation for autopsy is probably less strong in the elderly as physicians and family members may feel that the patient has "died of old age." A similar pattern of striking decline with advancing age was also observed by Ahronheim et al. However, they found that diagnostic errors made premortem as to the cause of death occurred almost twice as often in patients ≥ 70 years old as in patients < 70 years old.

Our discordance rate of 19.8% compares favorably with other autopsy studies. In our study, management would have been modified (class 1 errors) in 44% (8 of 18) of the discordant cases. Blosser et al reported that in 29.7% (11 of 37) of the patients, previously unknown findings would have changed therapy in the MICU had they been known before death.

Two previous autopsy studies of ICU patients found no relationship between the presence of diagnostic errors and either the length of ICU stay or patient age. Such findings are consistent with our observation. However, a recent autopsy study in a SICU reported that prolonged ICU stay (> 48 h) was associated with a higher likelihood of dying with an unestablished diagnosis. The majority of the discrepancies in diagnosis were infectious in nature, and occurred in the transplant surgical group. The

Table 3—Details of Class 1 Errors

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Diagnosis</th>
<th>Autopsy Diagnosis</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aspergillus and Klebsiella pneumonia, s/p double lung transplant for centrilobular emphysema</td>
<td>Acute bronchopneumonia with focal abscess formation (Aspergillus and Klebsiella), multiple pulmonary embolism with infarction, posttransplant T-cell lymphoma</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>2</td>
<td>Acute pancreatitis (post-ERCP)</td>
<td>Saddle pulmonary embolism</td>
<td>Thrombolitics/thrombectomy</td>
</tr>
<tr>
<td>3</td>
<td>Cardiac arrest secondary to ? tumor emboli from angiosarcoma of right ventricle</td>
<td>Endomyocardial fibrosis of right ventricle with associated thrombus and multiple thromboemboli to both lungs</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>4</td>
<td>Left lower lobe pneumonia, hypertension, diabetes mellitus, chronic renal failure, deep vein thrombosis on anticoagulation, history of thoracic and abdominal aortic aneurysm repair</td>
<td>Aortic dissection</td>
<td>Surgery</td>
</tr>
<tr>
<td>5</td>
<td>Right lower lobe pneumonia, GI bleed from gastric ulcers, coronary artery disease, diabetes mellitus, chronic obstructive lung disease</td>
<td>Perforated duodenal ulcer with peritonitis</td>
<td>Surgery</td>
</tr>
<tr>
<td>6</td>
<td>Acute pulmonary edema, hypertension, ischemic heart disease</td>
<td>Acute myocardial infarction</td>
<td>Thrombolytic therapy</td>
</tr>
<tr>
<td>7</td>
<td>Small cell lung cancer, bacterial pneumonia</td>
<td>Mycobacterial chelonae pneumonia</td>
<td>Antimycobacterial therapy</td>
</tr>
<tr>
<td>8</td>
<td>ARDS, community-acquired pneumonia</td>
<td>Hamman-Rich syndrome</td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

*ERCP = endoscopic retrograde; s/p = status post.
authors postulated that those patients who died quickly (≤ 48 h) typically died of the primary disease that prompted their admission to the SICU, thereby minimizing the occurrence of nosocomial colonization and infections, thus eliminating the majority of missed diagnoses.

Various studies have concluded that infection is one of the most frequently overlooked diagnosis, accounting for 25% of the misdiagnoses.1,27 Opportunistic infection may be overlooked, as it often coexists with other serious predisposing conditions. In our study, there was a suggestion that transplant

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Diagnosis</th>
<th>Autopsy Diagnosis</th>
<th>Reason for No Change in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Disseminated carcinoma of unknown primary</td>
<td>Poorly differentiated adenocarcinoma of lung</td>
<td>Advanced malignancy</td>
</tr>
<tr>
<td>10</td>
<td>Pneumonia, s/p resection of epithelioid hemangiopericytoma</td>
<td>Recurrent epithelioid hemangiopericytoma</td>
<td>Recurrent malignancy, no effective therapy</td>
</tr>
<tr>
<td>11</td>
<td>Sepsis from pneumonia, metastatic large cell undifferentiated carcinoma with unknown primary</td>
<td>Large cell undifferentiated carcinoma of left upper lobe with widespread metastases (pleural, left psoas muscle, lumbar spine, adrenals, pancreas, liver, bone marrow, large and small bowel)</td>
<td>Advanced malignancy</td>
</tr>
<tr>
<td>12</td>
<td>Shock liver (post CPR), pneumonia, s/p liver transplant for cryptogenic cirrhosis</td>
<td>Disseminated multiorgan candidasis</td>
<td>Empiric antifungal therapy</td>
</tr>
<tr>
<td>13</td>
<td>Multiorgan failure, ARDS, right lower lobe pneumonia, AFB and CMV positive, CMV bulky coat positive, s/p single lung transplant for emphysema, acute rejection, bronchiolitis obliterator obliterant obstructive pneumonia</td>
<td>Invasive aspergillosis of native and transplanted lungs, acute rejection by lung allograft, bronchiolitis obliterator of lung allograft</td>
<td>Empiric antifungal therapy, Withdrawal of life support</td>
</tr>
<tr>
<td>14</td>
<td>Septic shock (source unknown), deep vein thrombosis of left leg, diabetes mellitus, hypertension, coronary artery disease, active peptic ulcer disease</td>
<td>Bilateral large pulmonary emboli, diffuse large cell lymphoma of lungs</td>
<td>Inferior vena cava filter in situ, Anticoagulation contraindicated</td>
</tr>
<tr>
<td>15</td>
<td>Sepsis from ? meningitis, right cerebrovascular accident</td>
<td>Pneumonia</td>
<td>Empiric antibiotics</td>
</tr>
<tr>
<td>16</td>
<td>? pulmonary embolism from thrombosis of right internal jugular vein, pyelonephritis, diabetes mellitus, obstructive sleep apnea, morbid obesity</td>
<td>Acute-on-chronic pyelonephritis with left renal abscess</td>
<td>Appropriate antibiotics</td>
</tr>
<tr>
<td>17</td>
<td>Staphylococcus aureus septicemia, right hip arthritis, diabetes mellitus, obstructive sleep apnea, morbid obesity</td>
<td>Suppurative meningitis, suppurative osteomyelitis of lumbar vertebrae, lumbar spine and cauda equina, suppurative cellulitis, fasciitis cauda equina</td>
<td>Appropriate antibiotic</td>
</tr>
<tr>
<td>18</td>
<td>Congestive cardiac failure secondary to ischemic heart disease, polymyalgia rheumatica</td>
<td>Patchy myocardial necrosis secondary to severe myocardial</td>
<td>No effective therapy</td>
</tr>
</tbody>
</table>

Table 4—Details of Class 2 Errors*

*CPR = cardiopulmonary resuscitation; AFB = acid-fast bacilli; CMV = cytomegalovirus; see Table 3 legend for other abbreviation.
patients may be more prone to discordant diagnosis (43%), compared to the nontransplant patients (19%), but the difference was not statistically significant.

Pulmonary embolism (PE) has been the most common misdiagnosed condition in various studies. In this study, two patients (patients 2 and 14) died from massive PE that was not suspected clinically. Conversely, one patient (patient 16) was treated for presumed PE when it was not present. Another (patient 3) was thought to have tumor emboli from angiosarcoma of the right ventricle when he in fact had PE secondary to endomyocardial fibrosis. Goldman et al, in their retrospective study of 100 randomly selected autopsies from each of 3 decades, found that clinicians ascribed acute arrest more commonly to myocardial infarction in the 1960s and 1970s, and PE in the 1980s. This was due to the heightened awareness of the clinical problem of thromboembolism in recent years. Yet the percentage of missed cases of PE in autopsied patients had not changed.1

Clinically undiagnosed malignancies in autopsy-confirmed cases range from 18 to 35% in the years before 1970. After 1970, newer diagnostic techniques and improved clinical acumen from previous autopsy studies have contributed to a decline in the undiagnosed neoplastic diseases to as low as 4% in one series. In two patients (patients 1 and 14), the diagnosis of malignancy was missed completely. Two patients (patients 9 and 11) in our study had unknown primary site until necropsy. However, one patient (patient 3) was suspected of having malignancy when he did not. In two patients with known history of malignancies, active nontuberculous mycobacterial pulmonary infection was missed in one (patient 7), and pneumonia was diagnosed in another (patient 10) when she had recurrence of the malignancy.

Although the advancement of modern diagnostic capabilities led to improved premortem diagnosis, it also contributed to false-positive and false-negative results. Kirch and Schafii demonstrated, in their study of 100 randomly selected autopsies from each of the years 1959, 1969, 1979, and 1989, that the frequency of misdiagnoses (7%, 12%, 12%, and 11%) and false-positive diagnoses (7%, 11%, 9%, and 7%) remained unchanged, but the false-negative diagnoses increased from 24 to 34%. Although the new diagnostic procedures provide conclusive information in about 30% of cases, they also contributed to false-positive and false-negative diagnoses in 6 to 9% of cases. Another study by Landefeld et al reported that even the “gold standards” of coronary angiography and open-lung biopsy were occasionally misleading.

A review by Goldman of English-language literature between 1912 and 1980 also showed that the percentage of missed diagnoses had not decreased during this period. This does not indicate lack of progress in medical science, as the types of missed diagnoses varied in the different eras. During the period 1912 to 1965, 26 to 29% of bacterial pneumonias were missed clinically, but were rarely missed after 1970. In contrast, fungal and other unusual infectious agents were a more likely cause of misdiagnosed pneumonias in 1980. The rate of diagnostic discrepancy has remained relatively constant since the first autopsy study by Cabot in 1912. However, only the types of missed diagnoses changed. Advances in medical therapy such as organ transplantation and chemotherapy may prolong the lives of the patients and lead to new diseases, new complications, and opportunistic infections.

Unexpected findings at autopsy contribute to the increasing pool of medical knowledge and improved clinical acumen, which may lead to better patient care. Currently, only about 12% of the deaths in the United States are subject to autopsy. Much valuable information would be lost in the remaining nonautopsy cases. There is no direct monetary support for autopsy service in the existing health or life insurance policies or Medicare/Medicaid policies. A “complete” autopsy, which includes extensive gross and histologic examination of all body organs, may be ideal but not cost-effective in terms of financial and manpower resources. A “limited” autopsy may be performed to answer specific questions (“problem”-orientated autopsy). There are no reliable clinical predictors for high-diagnostic-yield autopsy cases. Cameron et al suggested the concept of “partial audit,” in which permission for autopsy be obtained on 20% of deaths, in addition to those which the clinicians would have selected because of “clinical interests” or “intrinsically difficult or puzzling” cases. A strategy to satisfy the investigational and educational needs, without incurring excessive demands on limited resources, would be to have partial audit and limited problem-orientated autopsies.

Limitations

This was a retrospective study, and judgments were made about classification of the diagnostic accuracy in each patient. In our study, the mean age in the autopsied patients was lower compared to those without autopsy; hence, the patients who had autopsy may not be representative of the critically ill patients in the MICU.
CONCLUSION

Advances in diagnostic technology have not diminished the value of autopsy. The discordance between the clinical cause of death and postmortem diagnosis was 19.8%. In 44.4% of the discordant cases, knowledge of the correct diagnosis would have altered therapy. Postmortem study can serve as a valuable monitor of quality control in diagnostic accuracy of MICU patients.

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