

Clinical autopsy: methodological applications and scientific perspectives in post-mortem diagnostics

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Summary

Objective. To analyze mortality from natural causes in hospital and out-of-hospital settings using clinical autopsy, emphasizing its methodological rigor and scientific contributions.

Methods. The present retrospective study included 1,340 autopsies conducted at the Umberto I General Hospital (2017-2023). Standardized protocols were applied, including complete autopsies, ancillary investigations (histopathology, imaging, microbiology, genetics), and systematic data collection.

Results. Out of 912 natural deaths, cardiac pathologies were the leading terminal cause (70.3%), followed by vascular (10.4%) and respiratory disorders (7.0%). Males (71%) predominated, with peak mortality between 55-74 years. Ancillary methods were crucial in identifying causes, particularly in individuals < 30 years where macroscopic findings were absent. Genetic studies helped identify hereditary cardiac conditions, enabling preventive family screening.

Conclusions. Clinical autopsy remains indispensable for determining the cause of death and improving diagnostic accuracy. A rigorous, standardized approach with ancillary methods enhances scientific understanding and public health interventions. Expanding post-mortem diagnostics and promoting centralized facilities is vital for quality mortality assessments.

Key words: mortality, clinical autopsy, natural death, post-mortem diagnosis, pathology

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Introduction

In 1705, a surge in sudden deaths in Rome prompted Pope Clement XI to commission the archiatrist, Giovanni Maria Lancisi, to conduct a medical investigation. Based on autopsy findings, Lancisi published *De Subitaneis Mortibus* in 1707, highlighting the link between sudden death and cardiac alterations, an insight remarkable for its time. Even today, sudden death remains a central focus in the medico-legal field, with forensic pathologists responsible for selecting the necessary investigations and formulating the cause of death.

Most sudden natural deaths are due to cardiovascular, respiratory, or neurological diseases, with coronary artery disease (CAD) being the leading cause. However, the true incidence of many causes remains unclear, particularly in countries where autopsies are infrequent. Yet, autopsies are essential when the cause of death is uncertain, even in individuals with known or suspected chronic illnesses.

Historically, autopsy has been regarded as the primary diagnostic tool for identifying the cause of death. Despite this, a decline in autopsy rates has been widely documented¹⁻³. Clinical autopsy must be considered the final step in the diagnostic process, conducted in a strictly scientific context using methods aimed at identifying anatomical, pathological, and clinical evidence on which physicians can base epicritical assessments. Given the complexity of sudden death, the preparation for an autopsy investigation must include comprehensive data, including clinical history (especially family history), death scene information, and medical records. Regardless of the validity of the diagnostic suspicion, the study of sudden death must always follow a rigorous approach. A complete autopsy remains fundamental. Sometimes, the autopsy identifies a macroscopic cause of death; other times, it does not provide sufficient information to determine the pathophysiological substrate of death, requiring ancillary investigations such as histopathological, radiological, toxicological, and, in certain cases, biomolecular analyses.

The main objective of the present study is to map mortality from natural causes in out-of-hospital and hospital settings through clinical autopsy.

The proposed research activity also aims to achieve the following secondary objectives:

- Outline a quality approach to clinical autopsy, focusing on technical aspects and integrating complementary diagnostic methods.
- Highlight the benefits of centralizing clinical autopsies for more complete diagnoses and classification of complex conditions.
- Contribute scientifically to the study of natural mortality in the medico-legal field.
- Demonstrate the value of clinical autopsy in completing diagnostic pathways and improving the quality of care⁴.

Materials and methods

STUDY POPULATION

The project was designed to study out-of-hospital and hospital mortality (in cases where an autopsy was requested) by analyzing clinical autopsies conducted at the Unit of Legal Medicine of the Umberto I General Hospital in Rome between 1 July 2017 and 30 June 2023. Specifically, the study group included:

- Subjects who died without receiving healthcare.
- Subjects who died in health facilities.
- Subjects who died of natural causes, without symptoms, or within 1 hour of acute symptom on-

set or rapid clinical deterioration.

- Subjects who died of natural causes but were alive within the previous 24 hours.
- Subjects who died of natural causes, where the death was not witnessed.

The exclusion criteria were:

- Subjects who died due to acute intoxication by toxic substances or narcotics.
- Subjects who died in a violent manner.

POST-MORTEM INVESTIGATIONS

In all cases, health information (Tab. I) and/or clinical documentation, including details of pre-existing pathologies, pharmacological therapies, diagnostic examinations, and previous surgical treatments, were collected in a timely manner.

The autopsy examination, in accordance with current protocols^{5,6}, involved a comprehensive investigation of all body cavities through a sequential approach (Tab. II). In all cases, immunoenzymatic screening of the urinary matrix was performed to exclude the presence of major substances of abuse and assess the exclusion criteria. The autopsy was conducted with the primary objective of determining:

- The natural cause of death, even if sudden.
- The nature and etiopathogenetic mechanisms of the pathology involved in the cause of death.

Table I. Fundamental elements of medical history.

Personal data	- Age - Gender - Nationality - Profession
Circumstantial data relating to the death	- Date - Time interval between the onset of symptoms and death - Place of death (home, work, hospital, etc.) - Circumstances (at rest, during sleep, during athletic or non-athletic physical exercise, during emotional stress) - Suspicious circumstances (immersion, road accident, intoxication, etc.) - Intervention of healthcare personnel
Family health history	- Pathologies of family members - Familiarity with particular conditions (sudden death in young individuals, arrhythmias, hereditary pathologies, unexplained syncope, etc.)
Remote and proximate pathological history	- General conditions - Previously diagnosed comorbidities - Previous surgical interventions - Previous laboratory and instrumental diagnostic tests - Congenital pathologies
Drug history	

Table II. Standardized autopsy workflow for the study of natural death.

External cadaveric examination	- Body weight and height (to correlate with heart weight and ventricular wall thickness). - Dysmorphic features (e.g. skin and appendages, skeletal anomalies). - Signs consistent with medical interventions. - Implantable defibrillators or pacemakers. - Scars from previous surgical procedures (identify and describe them in detail). - Skin injuries (identify and describe them in detail).
Complete autopsy with sequential approach	- Opening of the cranial cavity. - Dissection of the cervical region. - Opening of the thoracic, abdominal and pelvic cavities. - Any further dissections necessary to determine the cause of death.

- The potential hereditary nature of the identified pathological condition.

Autopsy has been based on “personalization” with technical choices tailored to diagnostic hypotheses, anatomical characteristics, and the preservation conditions of the corpses. Specifically, standardized methodologies such as the Rokitansky technique (in situ section of the viscera), the Virchow technique (organ-by-organ), the Ghon technique (en bloc), and the Letulle technique (en masse) were applied. If necessary, depending on the pathology and the risk of alteration during the procedures, the outlined techniques were combined with in situ anatomical dissection to highlight pathological findings. In cases of sudden death, post-mortem investigations followed a standardized approach, initially excluding extra-cardiac causes and then focusing on identifying possible cardiac causes. In the absence of macroscopic pathological findings (“mors sine materia”), determining the cause of death was deferred to subsequent diagnostic investigations.

Digital photography was deemed an essential component of post-mortem assessment. In all cases, comprehensive photographic documentation of both normal and pathological anatomy was collected. When the autopsy did not provide sufficient information for diagnostic conclusions, or when anamnestic data suggested a specific diagnostic suspicion, further investigations were conducted, including:

- In-toto organs examination after fixation in 10% neutral buffered formalin for an appropriate duration (approximately 14 days).
- Histopathological investigations using appropriate stains based on various diagnostic hypotheses,

aligned with available scientific evidence.

- Diagnostic imaging such as post-mortem Computed Tomography (PMCT) and post-mortem Magnetic Resonance Imaging (PMMR); in selected cases, after the fixation period, post-mortem Brain Magnetic Resonance (PMBMR) and post-mortem Cardiac Magnetic Resonance (PMCMR) on ex-situ organs.
- Microbiological investigations through direct testing and molecular biology analysis for pathogens such as *Listeria monocytogenes*, *Mycobacterium tuberculosis*, SARS-CoV-2, MERS-CoV, HBV, HCV, HIV, and Coxsackie.
- Genetic investigations.

DATABASE

The data were collected in a database specifically designed for the correlation study and divided into different sections (gender, age, nationality, date and place of death, medical history, autopsy, histology, diagnostic imaging, microbiology, genetics, and diagnosis of death). Regarding the diagnosis of death, in

Table III. System Organ Class (SOC).

SOC Index	Categories	SOC Index	Categories
1	Blood and lymphatic system disorders	15	Musculoskeletal and connective tissue disorders
2	Cardiac disorders	16	Neoplasms benign, malignant and unspecified (including cysts and polyps)
3	Congenital, familial and genetic disorders	17	Nervous system disorders
4	Ear and labyrinth disorders	18	Pregnancy, puerperium, and perinatal conditions
5	Endocrine disorders	19	Psychiatric disorders
6	Eye disorders	20	Renal and urinary disorders
7	Gastrointestinal disorders	21	Reproductive system and breast disorders
8	General disorders and administration site conditions	22	Respiratory, thoracic, and mediastinal disorders
9	Hepatobiliary disorders	23	Skin and subcutaneous tissue disorders
10	Immune system disorders	24	Social circumstances
11	Infections and infestations	25	Surgical and medical procedures
12	Injury, poisoning, and procedural complications	26	Vascular disorders
13	Investigations	27	Product issues
14	Metabolism and nutrition disorders		

cases where death did not occur immediately (in the absence of pre-existing pathological conditions), data relating to the entire causal sequence (initial, intermediate and terminal diagnosis of death) were recorded. The data were anonymized by assigning cases progressive numbers (NDI #).

Subsequently, numerical codes were assigned to the identified nosological entities (e.g., comorbidities and diagnoses of death) according to the System Organ Class (SOC) (Tab. III); terminal and initial diagnoses of death were classified respectively as “principal SOC” and “secondary SOC”.

STATISTICAL ANALYSIS

The statistical analysis was conducted upon completion of the data entry phase through the following steps:

- Measurement of categorical (nominal or ordinal) and quantitative (continuous or discrete) variables.
- Organization of data.
- Univariate descriptive statistics, including the calculating of mean, median, mode, standard deviation, and range.
- Bivariate and multivariate descriptive statistical analysis to explore relationships between variables using scatter plots, contingency tables, and correlation coefficients to assess associations.
- Evaluation of the main characteristics and statistical homogeneity of the selected sample using dis-

tribution tests and comparisons made with either Fisher's exact test or the chi-square test, depending on the case.

All statistical analyses were performed using R software, with the level of statistical significance set at 0.05.

Results

Out of 3,938 bodies admitted over 6 years (from 1 July 2017 to 30 June 2023) to the Unit of Legal Medicine at the Umberto I General Hospital in Rome, a total of 1,340 clinical autopsies were performed after excluding corpses under the jurisdiction of the Judicial Authority, those stored for hygienic-sanitary reasons, and those in transit to other facilities. Of these, 1,058 autopsies were conducted on individuals who died in out-of-hospital settings without healthcare assistance, while 282 were performed on individuals who died in public or private healthcare and social-healthcare facilities. At the conclusion of the dissections, excluding deaths attributable to violent causes, 912 individuals who died from natural causes were included in the present study.

From the data reported, it emerged that out of 912 deaths from natural causes during the study period, the male population was highly prevalent (952; 71%) compared to the female population (260; 29%). The

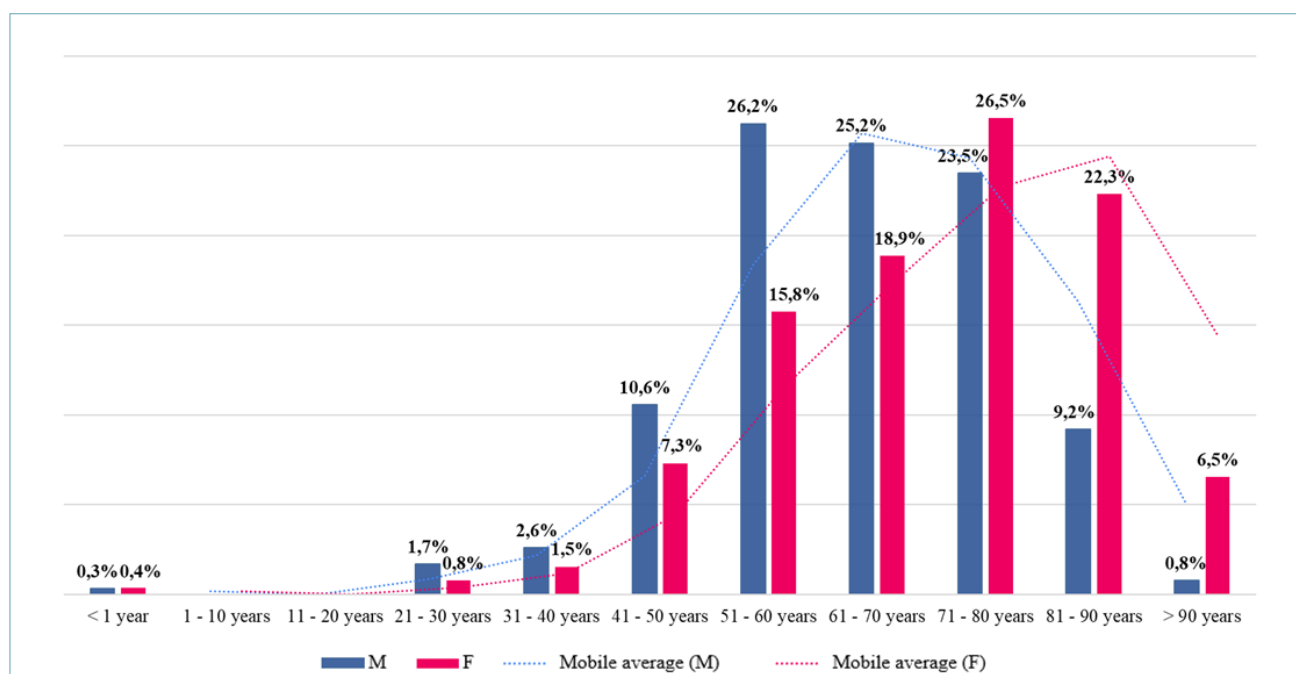


Figure 1. Age distribution percentage of the study population (relative frequency).

mean age at death was 65.45 years $\pm$ 14.50 SD (median 66 years; minimum age 0 years; maximum age 98 years). Among males, the mean age at death was 63.45 years $\pm$ 13.73 SD (median: 63.5 years; minimum: 0 years; maximum: 93 years). In contrast, among females, the mean age at death was 70.46 years $\pm$ 15.17 SD (median: 72.5 years; minimum: 0 years; maximum: 98 years).

The age distribution revealed that 13 (14.3%) subjects were under 30 years of age, 188 (20.6%) were between 30 and 54 years, 448 (49.1%) were between 55 and 74 years, and 263 (28.8%) were over 74 years of age. Specifically, approximately 75% of deaths among males occurred between the ages of 51 and 80, with the highest frequency between 51 and 60 years, compared to approximately 60% of deaths among females, with the highest frequency between 71 and 80 years (Fig. 1).

Regarding hospital deaths, the trend among males revealed a slightly increasing pattern between the ages of 51 and 80, while for females, there was a clear age-proportional increase, with a peak between 81 and 90 years.

Terminal causes of death were attributed to all enrolled cases (912; 100%), with a p-value of 0.038. Concerning the analysis of terminal causes of death, a predominance of cardiac disease was observed (641; 70.3%), followed by vascular (95; 10.4%), respiratory, thoracic, mediastinal (64; 7.0%), and gastrointestinal pathologies (46; 5.0%) (Fig. 2). The p-value related to terminal causes of death grouped according to the System Organ Class was 0.0667. The box plot

representation of terminal causes of death highlights a higher incidence of different diseases within the age range of 50 to 80 years (Fig. 3). The distribution of terminal causes of death by age group (Tab. IV), highlighted predominant mortality for nearly all disorders in the age group between 55 and 74 years. Among subjects aged 30 years or older, the most frequent terminal cause of death was cardiac, followed by vascular, respiratory, thoracic, mediastinal, and gastrointestinal disorders. Differently, among subjects under 30 years of age, deaths were more frequently attributed to cardiac diseases, followed by respiratory, thoracic, and mediastinal disorders.

About the gender distribution of terminal causes of death, cardiac diseases were prevalent in both genders (73.0% in males and 63.5% in females), followed by vascular diseases (8.3% in males and 15.8% in females), respiratory, thoracic, and mediastinal diseases (7.2% in males and 6.5% in females), and gastrointestinal diseases (5.4% in males and 4.2% in females).

In hospital deaths, the percentage distribution of terminal causes of death by healthcare setting (medical, surgical, emergency, and urgent care) highlighted that the most affected areas were the Emergency Departments.

Initial causes of death were attributed in 558 cases (61.2%), with a p-value less than 0.001. Regarding the initial causes of death, the results highlighted a preponderance of vascular disorders (308 cases; 55.2%) followed by cardiac disorders (96 cases; 17.2%) and infections and infestations (55 cases; 9.9%) (Fig. 4).

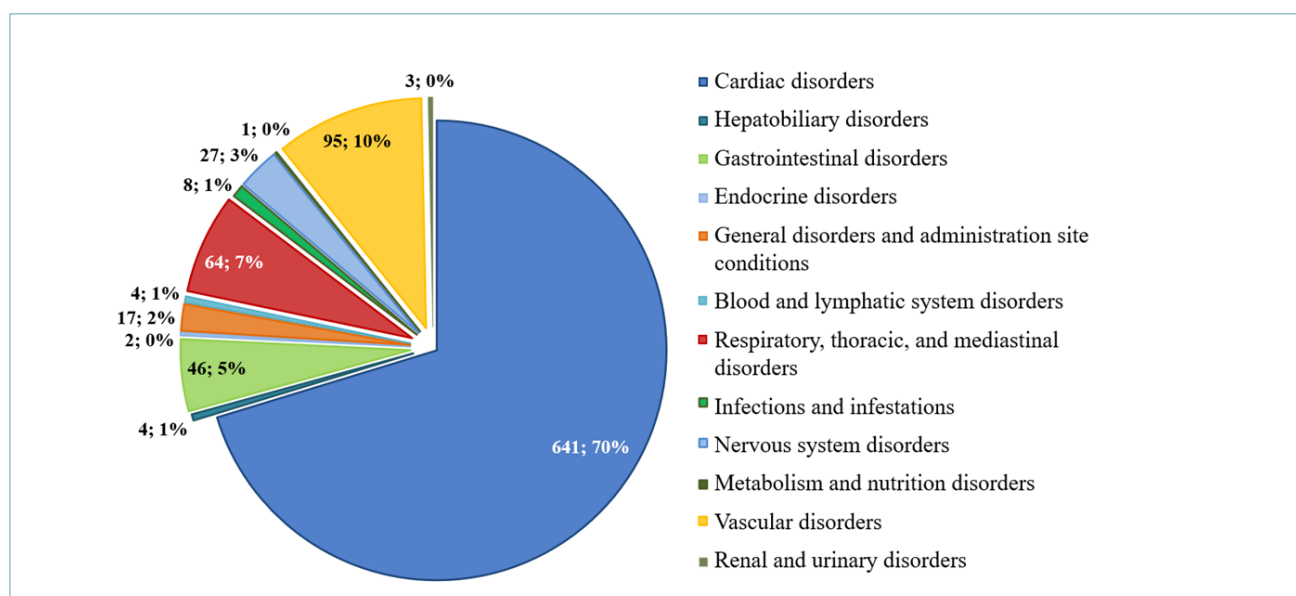


Figure 2. Terminal causes of death classified according to the System Organ Class.

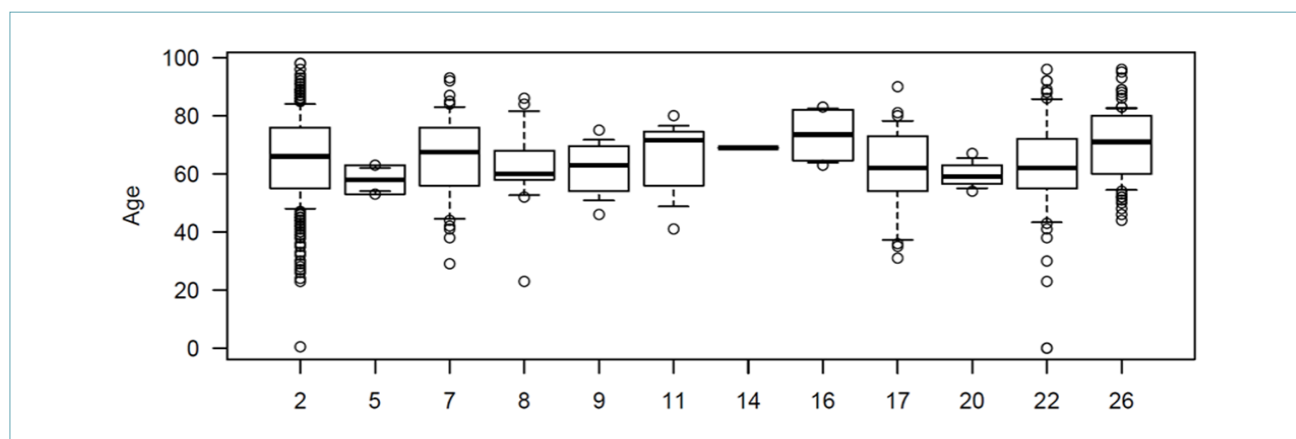


Figure 3. Graphical representation of the distribution of terminal causes of death in relation to age using a box plot.

Table IV. Distribution by age group of terminal causes of death.

Terminal cause of death	< 30 years	30-54 years	55-74 years	≥ 75 years
Cardiac disorders	8 (61.5%)	142 (75.5%)	304 (67.9%)	187 (71.1%)
Respiratory, thoracic, and mediastinal disorders	3 (23.1%)	12 (6.4%)	36 (8.0%)	13 (4.9%)
Gastrointestinal disorders	1 (7.7%)	10 (5.3%)	22 (4.9%)	13 (4.9%)
General disorders and administration site conditions	1 (7.7%)	2 (1.1%)	11 (2.5%)	3 (1.1%)
Hepatobiliary disorders		1 (0.5%)	2 (0.5%)	1 (0.4%)
Vascular disorders		10 (5.3%)	49 (10.9%)	36 (13.7%)
Endocrine disorders		1 (0.5%)	1 (0.2%)	
Infections and infestations		2 (1.1%)	4 (0.9%)	2 (0.8%)
Nervous system disorders		7 (3.7%)	14 (3.1%)	6 (2.3%)
Renal and urinary disorders		1 (0.5%)	2 (0.5%)	
Blood and lymphatic system disorders			2 (0.5%)	2 (0.8%)
Metabolism and nutrition disorders			1 (0.2%)	

The p-value related to initial causes of death grouped according to the System Organ Class was less than 0.001. The box plot representation of the initial causes of death showed a higher incidence of almost all diseases in the age group between 50 and 80 years (Fig. 5). Regarding congenital, familial, and genetic disorders, the highest incidence was recorded in the 30 to 45-year age group; conversely, for general disorders and administration site conditions, the highest incidence was observed in subjects over 80 years of age. The distribution by age group of the initial causes of death highlighted a predominant mortality for nearly all diseases between 55 and 74 years. In subjects aged 30 years and older, the analysis of initial causes of death shows a prevalence of vascular disorders, followed by cardiac disorders and infections and infestations. In the age group under 30 years, conditions related to pregnancy, puerperium, and perinatal conditions were predominant (Tab. V). The gender distribution demonstrated a predominance of vascular dis-

eases as initial cause of death in both males (35.1%) and females (30.8%).

The assessment of comorbidities revealed the presence of one comorbidity in 224 cases (43.2%), two comorbidities in 123 cases (23.7%), three comorbidities in 66 cases (12.7%), four comorbidities in 51 cases (9.8%), five comorbidities in 29 cases (5.6%), and six comorbidities in 24 cases (4.6%). In two cases (0.4%), death occurred in the absence of comorbidities.

Regarding the complementary investigations, histopathological examinations were deemed necessary in 273 cases (29.9%), microbiological investigations in 216 cases (23.8%), toxicological analyses in 89 cases (9.8%), radiological examinations in 34 cases (3.7%), and genetic investigations in 17 cases (1.9%). In terms of percentages, the age group most frequently subjected to further investigations was that of subjects under 30 years of age.

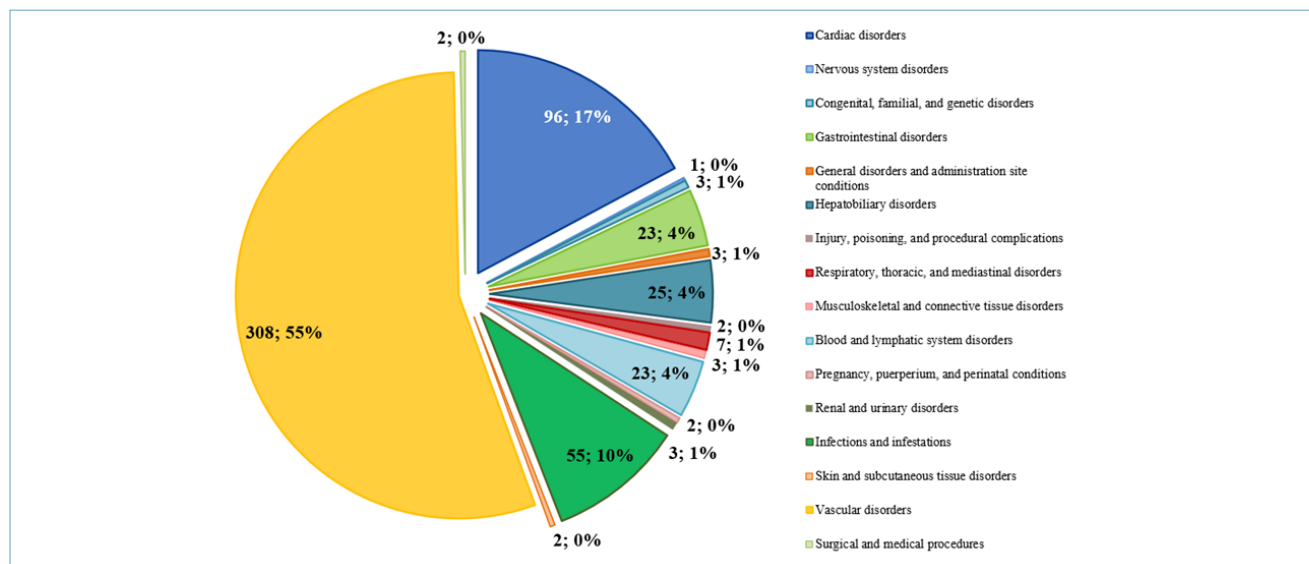


Figure 4. Initial causes of death classified according to the System Organ Class.

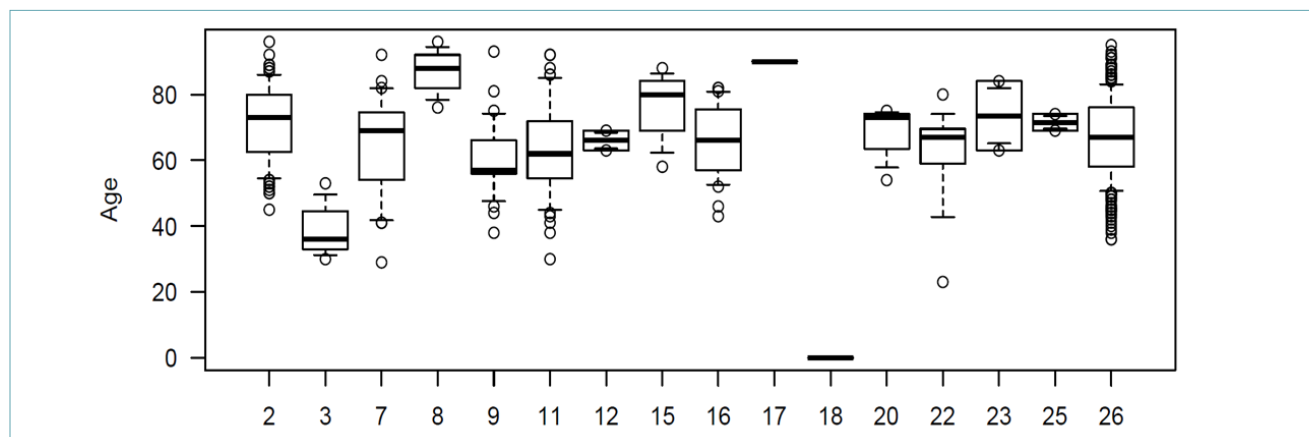


Figure 5. Graphical representation of the distribution of initial causes of death in relation to age using a box plot.

Table V. Distribution by age group of initial causes of death.

Initial cause of death	< 30 years	30-54 years	55-74 years	≥ 75 years
Pregnancy, puerperium, and perinatal conditions	2 (50.0%)			
Respiratory, thoracic, and mediastinal disorders	1 (25.0%)		5 (1.7%)	1 (0.6%)
Gastrointestinal disorders	1 (25.0%)	5 (4.9%)	11 (3.8%)	6 (3.7%)
Cardiac disorders		10 (9.8%)	43 (14.9%)	43 (26.4%)
General disorders and administration site conditions				3 (1.8%)
Hepatobiliary disorders		6 (5.9%)	16 (5.5%)	3 (1.8%)
Vascular disorders		60 (58.8%)	163 (56.4%)	85 (52.2%)
Infections and infestations		14 (13.7%)	30 (10.4%)	11 (6.8%)
Nervous system disorders				1 (0.6%)
Renal and urinary disorders		1 (1.0%)	1 (0.4%)	1 (0.6%)
Blood and lymphatic system disorders		3 (2.9%)	14 (4.8%)	6 (3.7%)
Congenital, familial and genetic disorders		3 (2.9%)		
Musculoskeletal and connective tissue disorders			1 (0.4%)	2 (1.2%)
Skin and subcutaneous tissue disorders			1 (0.4%)	1 (0.6%)
Surgical and medical procedures			2 (0.7%)	
Injury, poisoning, and procedural complications			2 (0.7%)	

Discussion

The present study demonstrates the usefulness of implementing mortality assessment tools in post-mortem diagnostics, which can also serve a preventive purpose for surviving family members.⁷ The results of the present study provide valuable insights into the collection, analysis, and communication of mortality data.

Post-mortem diagnostics play an essential role in public health surveillance by providing critical insights into mortality trends, contributing to the identification of emerging health threats, and enabling more accurate tracking of disease burdens within populations. Integrating post-mortem data into national health databases could improve the understanding of mortality patterns, especially for conditions that might not have been recognized or documented during life. Nevertheless, monitoring potential challenges or difficulties in applying different investigative methods adds depth to the research, providing a strong foundation for future updates and improvements.

The observed increase in clinical autopsies at Umberto I General Hospital, despite national declines, underscores the importance of maintaining high diagnostic standards.

Centralizing post-mortem investigations in specialized institutions and developing standardized training programs are essential to ensuring methodological consistency, especially as technological advances introduce new tools into routine diagnostics. Given these considerations, it is evident that reducing possible or uncertain diagnoses requires the adoption of a rigorous autopsy procedure, preceded by preliminary clinical data collection and supported by appropriate ancillary examinations.

Demographic data reveal a significant predominance of males and a lower average age at death among men. This evidence can be attributed to both health-related and social factors, such as lower health-seeking behavior and less adherence to preventive care among men compared to women. Additionally, various endogenous and exogenous factors likely contribute to the observed differences in life expectancy between genders.

Among deaths occurring in hospital settings, the predominance of those in Emergency Departments can be attributed to the inability to conduct comprehensive medical history and the lack of available documentation on pre-existing conditions⁸.

Regarding the causes of death, following data categorization according to the SOC classification system, the analysis highlighted:

- A significant predominance of mortality due to car-

diac and vascular causes in both genders, consistent with existing literature.

- A concentration of mortality for nearly all conditions within the age range of 55 to 74 years.
- An increase in diagnostic effectiveness and completeness associated with the use of ancillary methods.

The analysis of the initial, intermediate, and terminal causes of death showed p-values below the threshold of 0.05, thus demonstrating statistical significance. The increased p-value for the "primary SOC" is related to the heterogeneity of heart diseases, which vary significantly from one another and have different mortality rates; the box plot of terminal causes classified as "primary SOC" confirmed such heterogeneity, confirming that heart diseases span a wide mortality range. Further, the increased p-value for the "primary SOC", compared to the lower p-value for the "secondary SOC", reflects the pathophysiological mechanisms that, often in continuity with each other, lead to death from heart failure. Cardiac diseases are the terminal cause of death in 70.3% of the study population, despite being the initial cause in only 17.2% of cases. In contrast, vascular diseases, including coronary artery disease, account for 10.4% of terminal causes and 55.2% of initial causes. Infectious causes of death showed a significant decrease, being involved in 9.9% of deaths as the initial cause and only 0.9% as the terminal cause. In contrast, there was an increase of 5.7% in respiratory diseases (including bacterial and viral pneumonia) and 1.4% in systemic diseases (such as multiple organ dysfunction syndrome following sepsis).

Regarding the initial causes of death, in two cases, the secondary SOC was classified under "trauma, poisoning, and procedural complications." These cases were not excluded from the analysis, as they were not related to deaths resulting from traumatic events.

An additional clarification is needed regarding the quantitative discrepancy between the "primary SOC" and "secondary SOC", with the latter being numerically lower than the former. This discrepancy arises from the absence of a causal sequence in 354 cases; in other words, death in these cases occurred suddenly, with only a terminal cause and no identifiable initial cause.

The systematic comparison of the obtained results with the most recent epidemiological data from the Italian National Institute of Statistics provides interesting insights. While there is agreement regarding the frequency of deaths due to cardiac⁹, vascular, and respiratory diseases, discrepancies emerge for other conditions, such as neoplastic and cerebrovascular diseases. Such a difference is justified by the diagnos-

tic purpose of the assessment, as the neoplastic condition is often known and may be an incidental finding during autopsy. Furthermore, although cerebrovascular diseases rank among the most frequent causes of death in the general population, the present study revealed a frequency of 3% for primary SOC and 0.2% for secondary SOC. This incongruity is consistent with the frequent inability to obtain useful anamnesis (prior illnesses and symptoms leading to death) and with the diagnostic limitations of macroscopic evaluation of the brain.

Regarding the age of death associated with different diseases classified according to the SOC, concordance was found with epidemiological data and current scientific knowledge; almost all diseases showed a higher mortality rate in the age group between 55 and 74 years. Consistently, congenital, familial, and genetic diseases, as well as conditions related to perinatal issues, were correlated with a higher mortality rate in individuals under 45 years. The study of various causes of death by age revealed that the age at death is inversely proportional to the incidence of these causes, while it is directly proportional to the incidence of chronic, acute-on-chronic, and systemic diseases.

With specific reference to sudden deaths related to heart diseases that occur abruptly in youth, it is essential to highlight the necessity of a methodological approach focused on the study of the cardiac organ¹⁰. Indeed, ancillary investigations (such as post-mortem cardiac magnetic resonance imaging), examination of the organ after formalin fixation, histopathological studies, and genetic testing have enabled the identification of a definitive cause of death.

The present study highlighted the supportive role of ancillary methods in post-mortem diagnostic assessment for all cases warranting further investigation¹¹⁻¹⁴. Although histopathological analysis was performed in 273 out of 912 cases (29.9%), its selection was based on specific diagnostic suspicions or the absence of macroscopic findings. As such, standard histological sampling of all eviscerated organs was not uniformly implemented. Furthermore, analysis of the results regarding the number of examinations performed revealed that the age group most subjected to additional investigations (genetic, histopathological, microbiological, toxicological, and imaging diagnostics) was under 30 years. Regarding imaging diagnostics, despite the aforementioned data, 32 cases in the age group of 30 years or older underwent investigations (post-mortem computed tomography, post-mortem brain magnetic resonance, and post-mortem cardiac magnetic resonance) on cerebral and/or cardiac organs.

Additionally, given that the study period included the pandemic related to the spread of the SARS-CoV-2 vi-

rus, microbiological examinations were conducted on all corpses accepted from March 18, 2020, to September 30, 2022, regardless of diagnostic suspicion. Additionally, the total number of autopsies and the respective features were likely influenced by the COVID-19 pandemic, which imposed operational restrictions and altered the population of deceased individuals undergoing autopsy. The discussion of data related to autopsy activity in confirmed COVID-19 cases is therefore omitted to avoid introducing systematic biases related to the extraordinary conditions due to the pandemics; therefore, these deaths were recorded for completeness but were excluded from the analytical core of the study to maintain methodological consistency and avoid confounding effects.

The study under discussion not only provides a descriptive analysis of mortality phenomena but primarily highlights the advantages of promoting a culture of rigor and quality assessments in the field of *post-mortem* diagnostics¹⁵⁻¹⁷. The results obtained are undoubtedly preliminary and general, yet they are encouraging with regard to the extensive implementation and evaluation of effectiveness.

Post-mortem protocols should be adapted to incorporate cultural competence, ensuring that practices align with community values while maintaining scientific rigor.^{18,19} Additionally, education and outreach programs can help increase awareness about the importance of autopsies in understanding health conditions and preventing further deaths, thus fostering a more supportive environment for post-mortem procedures^{20,21}. Despite the valuable insights provided, some limitations should be acknowledged. First, the study may have been subject to biases in data collection, particularly when dealing with incomplete or inconsistent clinical records. Moreover, some cases may have lacked access to advanced diagnostic technologies, which could limit the completeness of the findings. Furthermore, although a comparative analysis with a previous similar time interval would have been valuable to identify potential peculiarities of the present series, no systematically collected or digitized data from that period are available at Umberto I General Hospital. Prior to 2017, autopsy records were maintained in heterogeneous formats, without standardized classification of cause-of-death data, ancillary investigations, or consistent inclusion criteria. This lack of accessible and structured historical data precluded a reliable comparison.

Future studies could address these limitations by improving data collection practices, ensuring access to a wider range of diagnostic tools, and standardizing procedures across multiple centers to enhance the generalizability of the results. Further research is also

needed to explore causes of death that were under-represented in the current study, such as neoplastic diseases and cerebrovascular conditions^{22,23}.

Finally, the findings allow for the formulation of recommendations concerning the autopsic evaluation and analysis of mortality. These recommendations can be summarized as follows:

- Adoption of a personalized autopsy approach tailored to clinical suspicion, supported by appropriate ancillary testing²⁴.
- Prioritize improvement actions for the implementation of post-mortem diagnostics and structured training programs²⁵.
- Extend the standardized investigative protocols to additional centers to enable broader data comparison and improve the public health impact of post-mortem assessments²⁶.

CONFLICTS OF INTEREST STATEMENT

The Authors have no conflicts of interest to disclose.

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AUTHORS' CONTRIBUTIONS

Conceptualization (M.P., M.S., and V.F.), Methodology (M.S., A.S., and V.F.), Supervision (V.F.), Investigation (M.P., M.S., F.M., D.M., G.P., V.G., and A.S.), Data curation (M.P., M.S., F.M., D.M., and G.P.), Formal analysis (M.P., M.S., and G.P.), Writing - Original draft (M.P., and F.M.), Writing - Review and editing (M.S.).

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