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Immunoreactivity of Cardiac Troponin, Myoglobin, and Caspase 3 revealing the connection of Acute myocardial Infarction with Acute Lung Injury in autopsied cases of sudden/ unexpected deaths.

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Abstract

Background: Sudden and unexplained deaths present challenges for forensic pathologists to determine underlying causes. Many disorders are cardiovascular in nature, although little research has been done on non-cardiac involvement, such as lung disease. This study investigates the correlation between acute myocardial infarction (AMI) and acute lung injury (ALI) in these types of fatalities.

Methods: This study examined 80 autopsy cases of unexpected or unexplained deaths that had been in Egypt between 2009 and 2014. Hematoxylin and eosin staining and immunohistochemistry employing cardiac markers such as troponin, myoglobin, and caspase 3 were used to examine lung and heart tissues.

Results: While 65% of individuals had additional lung diseases, about 35% of cases had signs of ALI. About 60% of people had coronary artery disease and 40% had cardiac muscle damage. Cases examined by HE & E showed no statistically significant relation or association between ALI and AMI cases. Unlike results with conventional staining, immunohistochemistry revealed a substantial correlation between mild indications of AMI and ALI.

Conclusion: The findings raise the possibility of myocardial damage associated ALI which by turn increases the incidence of sudden or unexpected deaths. For ALI patients, routine cardiac enzyme testing is advised to rule out cardiac involvement. Additional investigation into the pathways linking AMI and ALI is necessary.

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Key words acute lung injury, acute myocardial infarction, sudden unexpected death, autopsy

Introduction

Sudden and unexpected natural deaths pose challenges for forensic examiners to determine causes. Definitions for 'sudden' death vary from 30 mins to 24 hours after symptom onset as per different agencies like WHO, while 'unexpected' has separate connotations **(Albert et al. 2000).** The terms sudden and unexpected are not totally identical; these may have different connotations. The sudden death is not necessarily unexpected, and the unexpected

death is not necessarily sudden, but very often the two are in combination **(Shepherd 2003)**. Cardiac causes, mainly acute MI, lead the causes of sudden deaths statistically. However, the exact incidence rates of non-cardiac causes like acute lung pathologies is unclear owing to lack of systematic autopsies on such cases **(Maynard et al. 1993; De La Grandmaison and Durigon 2002; Kluakamkao et al. 2004)**.

Acute lung injury (ALI) was reclassified as mild or severe acute respiratory distress syndrome (ARDS), it continues to be a major cause of morbidity and death for patients who are sick. Many people classified as having ALI may have conditions ranging from refractory respiratory failure to transient dyspnea. Because patients with ALI diagnoses embark on significant clinical paths linked to better outcomes, it is still crucial to refine the diagnosis of ALI **(Bellani et al. 2016; Mowery et al. 2020).**

Prior studies established that AMI is linked with acute lung injury (ALI) in about 17% cases. The association worsens prognosis **(Milo et al. 2003; Cosentini et al. 2009 ; Van Den Berg et al. 2016).** Recommend testing for AMI in ALI cases presenting in emergency departments to improve outcomes. There is lack of data on the frequency and nature of acute inflammatory changes in the lungs that may accompany sudden cardiovascular deaths.

Studies on the relationship between ALI and AMI suggest that it may be just as significant as high pressure. Thus far, no publication has detailed any pulmonary abnormalities associated with potential inflammation in these patients **(De La Grandmaison 2006; Soeiro et al. 2012)**.

The primary objective of the current study is to minimize mortality rates and enhance therapeutic care for patients who come with acute respiratory failure by comprehending the correlation between simultaneous ALI and AMI in such unexpected fatalities. In addition, the study aims to reduce malpractice claims and medicolegal liability against physicians.

Material and Methods

This is a cohort retrospective study, delving into anonymized archives of sudden unexpected death cases referred to the Egyptian Forensic Medicine Authority (EFMA) between January 2009 and December 2014. Comprehensive autopsies had previously been conducted on all cases. A total of eighty cases were meticulously examined, analyzing preserved heart and lung tissue. The investigation spanned from January 2020 to January 2022, encompassing demographic information, available medical history, and autopsy findings.

Ethical consideration

After taken approval for this study from Research Ethics committee for Human and Animal Research at the Faculty of Medicine, Helwan University (**FMHU-REC**) (approval No: **46-2019**) and approval of Egyptian Forensic Medicine Authority **(EFMA)**.

Histopathological Study

Preserved blocks of lung and heart tissue sections from 80 autopsies of sudden or unexplained death cases, with or without evidence of acute myocardial infarction, referred to the pathology department of the Medico-legal Administration, Egypt, from 2009 to 2014. Heart tissue sections from coronaries and myocardia were processed, fixed in 10% neutral-buffered formalin, and embedded in paraffin. Histological sections were stained with hematoxylin–eosin.

Histologic sections were photographed in the Histology Department of the Faculty of Medicine, Ain Shams University. By using (Olympus BX-51;

Olympus, Tokyo Japan) with a digital Olympus camera (SC100, Japan) of 400 × magnification.

Seventy-three sections of myocardial tissue were selected for immunohistochemical staining. Histologic sections underwent immunohistochemistry with antibodies to human cTnT, MB depletion, and caspase 3 (Sigma-Aldrich, St. Louis, MO, USA) utilizing a standard avidin–biotin–peroxidase system.

Statistical analysis

The data were collected, revised, coded, and entered the Statistical Package for Social Science (IBM SPSS) version 23. Qualitative variables were presented as numbers and percentages. The comparison between groups with qualitative data was done using the Chi-square test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. Therefore, the p-value was considered significant as follows: ($P > 0.05$): Non-significant; ($P < 0.05$): Significant; ($P < 0.01$): Highly significant.

Results

Among the 80 sudden death cases examined, 63.8% (n=51) were male and 36.3% (n=29) were female, with ages ranging between 18-70 years across three designated categories. Residential data indicated 53.8% (n=43) were urban dwellers while 38.8% (n=31) resided rurally as shown in (**Table 1).**

Table 2 revealed the distribution of the etiological cause of death. Majority of cases died suddenly (47.5%), surgical related deaths were (28.8%), maternal mortality related deaths were (12.5%), and trauma related death were (11.3%) while reported organ failure leading to death results involved respiratory failure (68.8%), cardiac failure (20.0%) or combined cardiorespiratory (11.3%) organ systems failure.

Histopathological findings

Histopathological review revealed 95.0% of cases (n=76) exhibited significant lung pathology, categorized as either acute lung injury (ALI; 35.5%) or assorted other non-ALI pulmonary entities (64.5%) like thromboembolism, infections and trauma**.**

Histopathological alteration in lung tissues were discussed in (**Table 3, Figure 1)**. As in (**A**); showed in Showed a Junkie pneumopathy. A foreign body giant cell with plant tissues (Long arrow). The surrounding lung tissue shows features of DAD (intra-alveolar fibroinflammatory exudate with alveolar wall destruction (short arrow), and focal hemorrhages (dashed arrows) (×400). (**b**); showed a Septic bronchopneumonia. The lung tissue shows dense intra-alveolar mixed inflammatory reaction with pus cells, features of DAD (alveolar wall damage with hyaline membrane) (short arrow), and focal hemorrhages (dashed arrows), together with bacterial colonies (Long arrow) (×100). (**C**); showed an early ALI. The lung tissue shows severe congestion (dashed arrows) and entrapped granulocytes (short arrows). The long arrow points to an entrapped megakaryocyte (×400). (**D**); showed a Junkie pneumopathy, a foreign body giant cell with bone dust (long arrow). The surrounding lung tissue shows interalveolar hemorrhages (dashed arrows) (×400).

Myocardial tissue analysis detected abnormalities in 88.8% (n=71) specimens, ascribed to intrinsic cardiac muscle pathologies (40.8%) including infarction and inflammation or coronary arterial disease (59.2%) manifesting atherosclerosis and thromboses **(Table 4, Figure 2).**

Histopathological alteration in cardiac tissues were showed in **Figure 2**. As showed in (**A**); showed heart mural

thrombus, recent thrombus, luminal thrombus with lines of Zahn admixed with platelets and granulocytes (Long arrow) (×40). (**B**); showed advanced coronary atherosclerosis with severe (>75%) occlusion, and dystrophic calcifications (short arrows), associated with early luminal thrombus with (Long arrow) (×40). (**C**); showed neutrophilic myocarditis with moderate neutrophilic infiltrate (Long arrow) (×100). (**D**); showed eosinophilic myocarditis with eosinophilic infiltrate (Long arrow) (×100).

The study compares ALI cases and lung pathologies in terms of cardiac histopathology among the studied cases **(Table 5)** shows no statistically significant difference between both groups with conventional stain. Also, Comparison between ALI patients and patients with other pathologies regarding heart pathology shows no statistically significant difference between both groups.

A Comparison between ALI patients and patients with other pathologies regarding cardiac muscle pathology shows most cases of ALI patients had Acute myocardial infarction (55.6%) of cases while myocarditis was more common in cases with other pathologist in the lung, but the results did not reach statistically significant difference between both groups.

A relation between ALI patients and patients with other pathologies regarding coronary pathology shows atherosclerosis was found in most cases of ALI (66.7%) and in other pathologies in the lungs (54.2%) respectively, with no statistically significant difference between both groups.

Immunohistochemical findings

Targeted immunohistochemistry was undertaken on 73 samples using cardiac markers troponin, myoglobin and caspase 3 to ascertain early ischemic insult unapparent on conventional histology **(Table 6).** Comparative testing indicated significant associations between ALI and troponin (p=0.000) as well as myoglobin (p=0.001) depletion, along with caspase 3 expression (p=0.016), indicative of higher grade ischemic myocardial injury in the ALI subgroup **(Tables 7, 9, 12).**

As showed in **table 6** shows that there is statistically significant difference found between ALI group and other pathologies group regarding immunoreactivity of troponin with p-value = 0.000.

Immunoreactivity of the three cardiac stains troponin, myoglobin and caspase 3 were done on 73 cases out of 80 total number of cases in this study **(Figure 3).**

The troponin depletion in cardiac muscle as shown in **Figure 3 (A)** was marked in most cases of ALI group (44.4%) while focal and no loss of troponin in cardiac muscle were mostly appear in cases of other pathologies in lung with equal percentage (32.6%).

The myoglobin depletion in cardiac muscle as shown in **Figure 3 (B)** and its relationship with pulmonary histopathologic changes shows statistically significant difference between them with p-value = 0.001. Marked loss in myoglobin stain was found in most cases of ALI (48.1%) while focal loss was found in most cases of other pathologies in lung (32.2%) of cases.

Diffuse strong reaction of caspase 3 stain in cardiac muscles as shown in **Figure 3 (C)** was found in (51.9%) of ALI group, while Focal positive cytoplasmic reaction was recorded in other pathologies in lung (44.2%). There is statistically significant difference found between both groups regarding caspase 3 stain reaction in the cardiac muscle with p-value = 0.016.

Therefore, advanced immunohistochemical tissue analytics delineated a substantive correlation and

mechanistic nexus between acute lung and cardiac damage unrecognized on preliminary histological examination in these selected sudden fatality cases that warrants further investigation.

Relation between Troponin marker and Presence of pulmonary histopathology among the studied cases.

As showed in **table 7**, the relation between troponin stain depletion in cardiac muscle and pulmonary histopathologic changes shows statistically significant difference with p-value = 0.000 between ALI and other pathologies in lung groups.

No loss of troponin stain in cardiac muscle tissue was (14 cases; 93.3%) in other pathologies in lung group and (3 case; 17.6%) in ALI group. Focal loss of troponin stain in cardiac muscle tissue was (14 cases; 82.4%) in other pathologies in lung group and (1 case; 6.7%) in ALI group. Moderate loss of troponin stain in cardiac muscle tissue was (11 cases; 50.0%) equal percentage in both other pathologies in lung group and in ALI group.

Marked loss of troponin stain in cardiac muscle tissue was (12 cases; 75.0%) in ALI group and (4 cases; 25.0%) in other pathologies in lung group.

Relation between Troponin marker and other pathologies in the lung among the studied cases.

As discussed in **table 8**, the relation between troponin stain depletion in cardiac muscle and in other pathologies in lung group shows statistically no significant difference.

No loss of troponin stain in cardiac muscle tissue was found (4 cases; 28.6%) in pulmonary embolism group, (3 cases; 21.4%) in bronchopneumonia group, (2 cases; 14.3%) equal percentage in acute pulmonary edema group and traumatic pulmonary hemorrhage group, (1 case; 7.1%) equal percentage in Junkie pneumopathy group, Granuloma group and COPD group.

Focal loss of troponin stain in cardiac muscle tissue was found (5 cases; 35.7%) in Junkie pneumopathy group, (4 cases; 28.6%) in pulmonary embolism group, (2 cases; 14.3%) equal percentage in bronchopneumonia group and granuloma group, (1 case; 7.1%) in traumatic pulmonary hemorrhage group.

Moderate loss of troponin stain in cardiac muscle tissue was found (5 cases; 45.5%) in bronchopneumonia group, (3 cases; 27.3%) in Junkie pneumopathy group, (1 case; 9.1%) equal percentage in pulmonary embolism group, granuloma group and COPD group.

Marked loss of troponin stain in cardiac muscle tissue was found (2 cases; 50.0%) in pulmonary embolism group, and (1 case; 25.0%) equal percentage in granuloma group and acute pulmonary edema group.

Relation between myoglobin marker and pulmonary histopathologic changes among the studied cases.

As discussed in **table 9**, the relation between myoglobin stain depletion in cardiac muscle and pulmonary histopathologic changes shows statistically significant difference with p-value = 0.001.

No loss of myoglobin stain in cardiac muscle tissue was (11 cases; 78.6%) in other pathologies in lung group while it was (3 case; 21.4%) in ALI group.

Focal loss of myoglobin stain in cardiac muscle tissue was (14 cases; 93.3%) in other pathologies in lung group while it was (1 case; 6.7%) in ALI group.

Moderate loss of myoglobin stain in cardiac muscle tissue was (13 cases; 56.5%) in other pathologies in lung while it was (10 cases; 43.5%) in ALI groups.

Marked loss of myoglobin stain in cardiac muscle tissue was (13 cases; 72.2%)

in ALI group while it was (5 cases; 27.8%) in other pathologies in lung group.

Relation between Myoglobin marker and ALI cases group among the studied cases.

As discussed in **table 10**, the relation between myoglobin stain depletion in cardiac muscle and ALI shows nearly statistically significant difference with p-value = 0.069.

No loss of myoglobin stain in cardiac muscle tissue was found (3 cases; 100%) in diffuse alveolar damage group.

Focal loss of myoglobin stain in cardiac muscle tissue was found (1 case; 100%) in Diffuse alveolar damage with eosinophilic lung disease group. Moderate loss of myoglobin stain in cardiac muscle tissue was found (8 cases; 80.0%) in diffuse alveolar damage group while it was (2 cases; 20.0%) in Diffuse alveolar damage with eosinophilic lung disease group.

Marked loss of myoglobin stain in cardiac muscle tissue was found (12 cases; 92.3%) in diffuse alveolar damage case group and (1 case; 7.7%) in end stage interstitial lung disease group.

Relation between Myoglobin marker and other pathologies in lung among the studied cases.

As discussed in **table 11**, the Relation between myoglobin stain depletion in cardiac muscle and in other pathologies in lung group shows statistically no significant difference.

No loss of myoglobin stain in cardiac muscle tissue was found (4 cases; 36.4%) in pulmonary embolism group, (3 cases; 27.3%) in bronchopneumonia group, (2 cases; 18.2%) in traumatic pulmonary hemorrhage group, and (1 case; 9.1%) equal percentage in granuloma group and acute pulmonary edema group.

Focal loss of myoglobin stain in cardiac muscle tissue was found (5 cases; 35.7%) in Junkie pneumopathy group, (4 cases; 28.6%) in pulmonary embolism group, (2 cases; 14.3%) equal percentage in bronchopneumonia group and granuloma group, (1 case; 7.1%) in traumatic pulmonary hemorrhage group.

Moderate loss of myoglobin stain in cardiac muscle tissue was found (5 cases; 38.5%) in bronchopneumonia group, (3 cases; 23.1%) in Junkie pneumopathy group, (2 case; 15.4%) in COPD group, (1 case; 7.7%) equal percentage in pulmonary embolism group, granuloma group and acute pulmonary edema.

Marked loss of myoglobin stain in cardiac muscle tissue was found (2 cases; 40.0%) in pulmonary embolism group, (1 case; 20.0%) equal percentage in Junkie pneumopathy group and granuloma group.

Relation between Caspase 3 marker and Pulmonary histopathologic changes among the studied cases.

As discussed in **table 12**, the relation between caspase 3 stain reaction in cardiac muscle and pulmonary histopathologic changes shows statistically significant difference with p-value = 0.016.

Focal positive cytoplasmic reaction of caspase 3 stain in cardiac muscle tissue was found (19 cases; 82.6%) in other pathologies in lung group while it was (4 cases; 17.4%) in ALI group.

Moderate positive cytoplasmic reaction of caspase 3 stain in cardiac muscle tissue was found (14 cases; 60.9%) in other pathologies in lung group while it was (9 cases; 39.1%) in ALI group.

Diffuse strong positive reaction of caspase 3 stain in cardiac muscle tissue was found (14 cases; 58.3%) in ALI group while it was (10 cases; 41.7%) in other pathologies in lung group.

Relation between Caspase 3 marker and ALI group among the studied cases.

As illustrated in **table 13**, the relation between caspase 3 cytoplasmic reaction in cardiac muscle and ALI shows

no statistically significant difference between them.

Focal positive cytoplasmic reaction of caspase 3 stain in cardiac muscle tissue was found (3 cases; 75.0%) in diffuse alveolar damage group and (1 case; 25.0%) in Diffuse alveolar damage with eosinophilic lung disease group.

Moderate positive cytoplasmic reaction of caspase 3 stain in cardiac muscle tissue was found (7 case; 77.8%) in Diffuse alveolar group, (1 case; 11.1%) equal percentage in diffuse alveolar damage with eosinophilic lung disease group and end stage interstitial lung disease group.

Diffuse strong positive reaction of caspase 3 stain in cardiac muscle tissue was found (13 cases; 92.9%) in diffuse alveolar damage case group, and (1 case; 7.1%) in diffuse alveolar damage with eosinophilic lung disease group.

Relation between Caspase 3 marker and other pathologies in lung group among the studied cases.

As showed in **table 14**, the Relation between caspase 3 stain reaction in cardiac muscle and in other pathologies in lung group shows statistically no significant difference.

Focal positive cytoplasmic reaction of caspase 3 stain in cardiac muscle tissue was (6 cases; 31.6%) in pulmonary embolism group, (4 cases; 21.1%) in bronchopneumonia group, (3 cases; 15.8%) in Junkie pneumopathy group, (2 cases; 10.5%) equal percentage in granuloma group and traumatic pulmonary hemorrhage group, (1 case; 5.3%) equal percentage in acute pulmonary edema group and COPD group.

Moderate positive cytoplasmic reaction of caspase 3 stain in cardiac muscle tissue was (5 cases; 35.7%) in Junkie pneumopathy group, (3 cases; 21.4%) in granuloma group, (2 cases; 14.3%) equal percentage in pulmonary embolism group and bronchopneumonia group and, (1 case; 7.1%) equal percentage in acute pulmonary edema group and traumatic pulmonary hemorrhage group.

Diffuse strong positive reaction of caspase 3 stain in cardiac muscle tissue was (4 cases; 40.0%) in bronchopneumonia group, (3 cases; 30.0%) in pulmonary embolism group, (1 case; 10.0%) equal percentage in Junkie pneumopathy group, acute pulmonary edema group, and COPD group.

Table (1): Distribution of demographic data of the studied 80 cases.

		No.	**%**
Gender	Male	51	63.8%
	Female	29	36.3%
Residence	Urban	43	53.8%
	Rural	31	38.8%
	Un available	6	7.5%
Age	18-30	20	25.0%
	31-50	45	56.3%
	51-70	15	18.8%

Table (2): Distribution of the etiological cause of death and reported organ failure leading to death among the studied 80 cases.

		No.	%
Etiological cause of death	Sudden death (SD)	38	47.5%
	Surgical related	23	28.8%
	Maternal mortality related	10	12.5%
	Trauma related	9	11.3%
Reported organ failure leading to death	Respiratory Failure	55	68.8%
	Cardiac Failure	16	20.0%
	Cardiorespiratory Failure (General Pathology)	9	11.3%

Table (3): Distribution of pulmonary histopathology results of the studied 80 cases.

Presence of Pulmonary histopathology	**No.**	**%**
Yes	76	95.0%
No remarkable pathology	4	5.0%
Pulmonary histopathologic changes		
ALI	**27**	**35.5%**
DAD	23	85.2%
DAD + Eosinophilic lung disease	3	11.1%
End stage Interstitial lung disease	1	3.7%
Other pathologies	**49**	**64.5%**
Embolism	14	28.6%
Bronchopneumonia	11	22.4%
Junkie pneumopathy	9	18.4%
Granuloma (T.B & sarcoidosis)	7	14.3%
Acute pulmonary edema	3	6.1%
Pulmonary hemorrhage (Traumatic)	3	6.1%
COPD	2	4.1%

ALI: Acute lung injury

DAD: Diffuse alveolar damage

Table (4): Distribution of cardiac histopathology results among the studied cases.

Presence of cardiac histopathology	**No.**	**%**
No abnormality detected	9	11.3%
Yes	71	88.8%
Heart pathology		
Cardiac muscle pathology	**29**	**40.8%**
IHD (AMI)	10	34.5%
Myocarditis (eosinophilic, neutrophilic, lymphocytic)	10	34.5%
Cardiomyopathy	4	13.8%
Pericardial hemorrhage and Pericarditis	3	10.3%
Infective endocarditis	1	3.4%
Granulomatous myocarditis (sarcoidosis)	1	3.4%
Coronary pathology	**42**	**59.2%**
Atherosclerosis	24	57.1%
ACS (thrombus, hemorrhage in atheroma, ruptured atheroma)	13	31.0%
Congenital coronary bridging	4	9.5%
Fibromuscular dysplasia	1	2.4%

Table (5): Chi-square test X^2 showing comparison between ALI cases group and other pathologies in lung cases group regarding the presence of cardiac histopathology with conventional stain among the studied cases**.**

Presence of cardiac histopathology		Pulmonary histopathologic changes				X^2	P	Sig.
		ALI		Other pathologies				
		No.	%	No.	%			
No abnormality detected		**3**	11.1%	6	12.2%	0.021	0.884	NS
Yes		**24**	88.9%	43	87.8%			
Heart pathology	**No abnormality detected**	**3**	11.1%	6	12.2%	0.306	0.858	NS
	Cardiac muscle pathology	**9**	33.3%	19	38.8%			
	Coronary pathology	**15**	55.6%	24	49.0%			
Cardiac muscle pathology	**Cardiomyopathy**	**1**	11.1%	3	15.8%	3.471	0.482	NS
	IHD (AMI)	**5**	55.6%	5	26.3%			
	Myocarditis (eosinophilic, neutrophilic, lymphocytic)	**3**	33.3%	7	36.8%			
	Pericardial Hemorrhage and Pericarditis	**0**	0.0%	3	15.8%			
	Infective endocarditis	**0**	0.0%	0	0.0%			
	Granulomatous myocarditis (sarcoidosis)	**0**	0.0%	1	5.3%			
Coronary pathology	**ACS (thrombus, hemorrhage in atheroma, ruptured atheroma)**	**3**	20.0%	8	33.3%	2.733	0.435	NS
	Atherosclerosis	**10**	66.7%	13	54.2%			
	Congenital coronary bridging	**1**	6.7%	3	12.5%			
	Fibromuscular dysplasia	**1**	6.7%	0	0.0%			

P-value >0.05: Nonsignificant

Table (6): Distribution of immuno-reactivity of cardiac stains among the studied cases**.**

Immuno-reactivity of cardiac stains		No.	%
Troponin	No loss	16	21.9%
	Focal loss	17	23.3%
	Moderate loss	23	31.5%
	Marked loss	17	23.3%
Myoglobin	No loss	15	20.5%
	Focal loss	15	20.5%
	Moderate loss	23	31.5%
	Marked loss	20	27.4%
Caspase 3	Focal positive cytoplasmic reaction	24	32.9%
	Moderate positive cytoplasmic reaction	24	32.9%
	Diffuse strong reaction	25	34.2%

Table (7): Chi-square test X^2 showing relation between Troponin marker and Presence of pulmonary histopathology among the studied cases.

Presence of pulmonary histopathology		Troponin								X^2	P	Sig.
		No loss		Focal loss		Moderate loss		Marked loss				
		No.	%	No.	%	No.	%	No.	%			
Pulmonary histopathologic changes	ALI	1	6.7%	3	17.6%	11	50.0%	12	75.0%	19.760	0.000	HS
	Other pathologies	14	93.3%	14	82.4%	11	50.0%	4	25.0%			

P-value< 0.01: highly significant

ALI: Acute lung injury

Table (8): Chi-square test X^2 showing relation between Troponin marker and other pathologies in the lung among the studied cases.

Presence of pulmonary histopathology		Troponin								X^2	P	Sig.
		No loss		Focal loss		Moderate loss		Marked loss				
		No.	%	No.	%	No.	%	No.	%			
Other pathologies	Embolism	4	28.6%	4	28.6%	1	9.1%	2	50.0%	19.038	0.389	NS
	Junkie pneumopathy	1	7.1%	5	35.7%	3	27.3%	0	0.0%			
	Bronchopneumonia	3	21.4%	2	14.3%	5	45.5%	0	0.0%			
	Granuloma (T.B & sarcoidosis)	1	7.1%	2	14.3%	1	9.1%	1	25.0%			
	Acute pulmonary edema	2	14.3%	0	0.0%	0	0.0%	1	25.0%			
	COPD	1	7.1%	0	0.0%	1	9.1%	0	0.0%			
	Pulmonary hemorrhage (Traumatic)	2	14.3%	1	7.1%	0	0.0%	0	0.0%			

P-value >0.05: Nonsignificant

Table (9): Chi-square test X^2 showing relation between myoglobin marker and pulmonary histopathologic changes among the studied cases.

Presence of pulmonary histopathology		Myoglobin								X^2	P	Sig.
		No loss		Focal loss		Moderate loss		Marked loss				
		No.	%	No.	%	No.	%	No.	%			
Pulmonary histopathologic changes	**ALI**	3	21.4%	1	6.7%	10	43.5%	13	72.2%	17.017	0.001	HS
	Other pathologies	11	78.6%	14	93.3%	13	56.5%	5	27.8%			

P-value< 0.01: highly significant

ALI: Acute lung injury

Table (10): Chi-square test X^2 showing relation between Myoglobin marker and ALI cases group among the studied cases.

Presence of pulmonary histopathology		Myoglobin								X^2	P	Sig.
		No loss		Focal loss		Moderate loss		Marked loss				
		No.	%	No.	%	No.	%	No.	%			
ALI	DAD	3	100.0%	0	0.0%	8	80.0%	12	92.3%	11.715	0.069	NS
	DAD + Eosinophilic lung disease	0	0.0%	1	100.0%	2	20.0%	0	0.0%			
	End stage Interstitial lung disease	0	0.0%	0	0.0%	0	0.0%	1	7.7%			

P-value >0.05: Nonsignificant
ALI: Acute lung injury
DAD: Diffuse alveolar damage

Table (11): Chi-square test X^2 showing relation between Myoglobin marker and other pathologies in lung among the studied cases.

Presence of pulmonary histopathology		Myoglobin								X^2	P	Sig.
		No loss		Focal loss		Moderate loss		Marked loss				
		No.	%	No.	%	No.	%	No.	%			
Other pathologies	Embolism	4	36.4%	4	28.6%	1	7.7%	2	40.0%	20.137	0.325	NS
	Junkie pneumopathy	0	0.0%	5	35.7%	3	23.1%	1	20.0%			
	Bronchopneumonia	3	27.3%	2	14.3%	5	38.5%	0	0.0%			
	Granuloma (T.B & sarcoidosis)	1	9.1%	2	14.3%	1	7.7%	1	20.0%			
	Acute pulmonary edema	1	9.1%	0	0.0%	1	7.7%	1	20.0%			
	COPD	0	0.0%	0	0.0%	2	15.4%	0	0.0%			
	Pulmonary hemorrhage (Traumatic)	2	18.2%	1	7.1%	0	0.0%	0	0.0%			

P-value >0.05: Nonsignificant

Table (12): Chi-square test X^2 showing relation between Caspase 3 marker and Pulmonary histopathologic changes among the studied cases.

Presence of pulmonary histopathology		Caspase 3						X^2	P	Sig.
		Focal positive cytoplasmic reaction		Moderate positive cytoplasmic reaction		Diffuse strong reaction				
		No.	%	No.	%	No.	%			
Pulmonary histopathologic changes	ALI	4	17.4%	9	39.1%	14	58.3%	8.313	0.016	S
	Other pathologies	19	82.6%	14	60.9%	10	41.7%			

P-value <0.05: Significant

ALI: Acute lung injury

Table (13): Chi-square test X^2 showing relation between Caspase 3 marker and ALI group among the studied cases.

Presence of pulmonary histopathology		Caspase 3						X^2	P	Sig.
		Focal positive cytoplasmic reaction		Moderate positive cytoplasmic reaction		Diffuse strong reaction				
		No.	%	No.	%	No.	%			
ALI	DAD	3	75.0%	7	77.8%	13	92.9%	3.096	0.542	NS
	DAD + Eosinophilic lung disease	1	25.0%	1	11.1%	1	7.1%			
	End stage Interstitial lung disease	0	0.0%	1	11.1%	0	0.0%			

P-value >0.05: Nonsignificant

ALI: Acute lung injury

DAD: Diffuse alveolar damage

Table (14): Chi-square test X^2 showing relation between Caspase 3 marker and other pathologies in lung group among the studied cases.

Presence of pulmonary histopathology		Caspase 3						X^2	P	Sig.
		Focal positive cytoplasmic reaction		Moderate positive cytoplasmic reaction		Diffuse strong reaction				
		No.	%	No.	%	No.	%			
Other pathologies	Embolism	6	31.6%	2	14.3%	3	30.0%	9.918	0.623	NS
	Junkie pneumopathy	3	15.8%	5	35.7%	1	10.0%			
	Bronchopneumonia	4	21.1%	2	14.3%	4	40.0%			
	Granuloma (T.B & sarcoidosis)	2	10.5%	3	21.4%	0	0.0%			
	Acute pulmonary edema	1	5.3%	1	7.1%	1	10.0%			
	COPD	1	5.3%	0	0.0%	1	10.0%			
	Pulmonary hemorrhage (Traumatic)	2	10.5%	1	7.1%	0	0.0%			

P-value >0.05: Nonsignificant

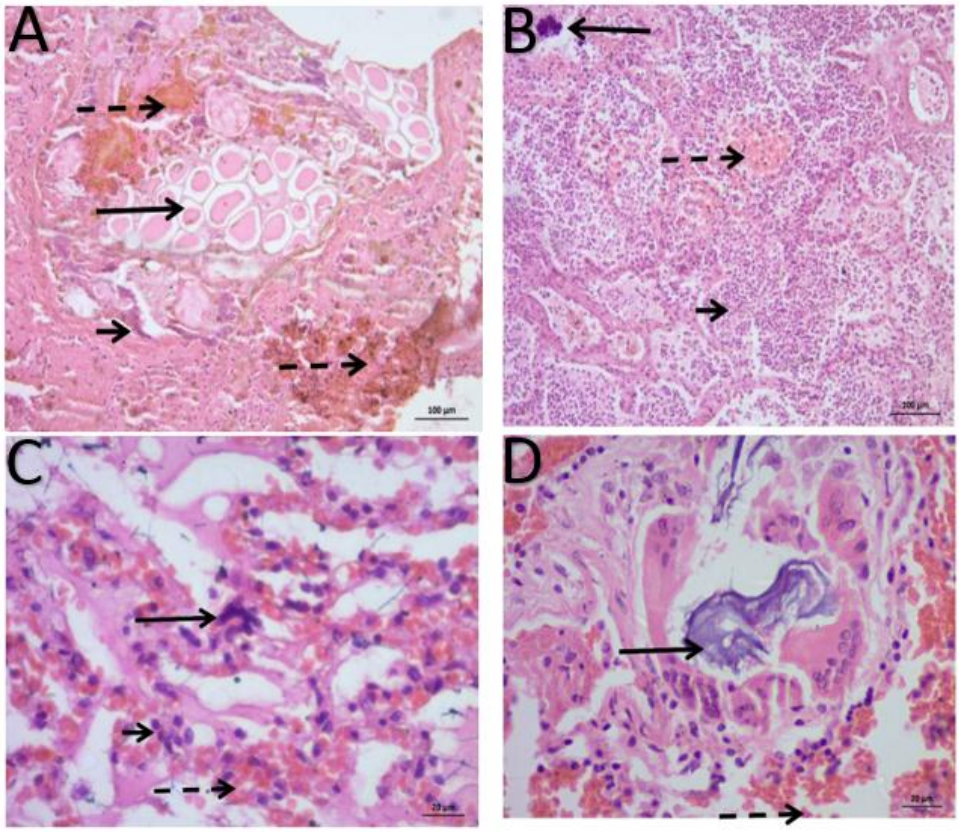

Figure (1): Photomicrograph of human lung tissue (Hx & E) stained sections. (A) Showed a Junkie pneumopathy. A foreign body giant cell with plant tissues (Long arrow). The surrounding lung tissue shows features of DAD (intra-alveolar fibroinflammatory exudate with alveolar wall destruction (short arrow), and focal hemorrhages (dashed arrows) (×400). **(B)** showed a septic bronchopneumonia. The lung tissue shows dense intra-alveolar mixed inflammatory reaction with pus cells, features of DAD (alveolar wall damage with hyaline membrane) (short arrow), and focal hemorrhages (dashed arrows), together with bacterial colonies (Long arrow) (×100). **(C)** showed an early ALI. The lung tissue shows severe congestion (dashed arrows) and entrapped granulocytes (short arrows). The long arrow points to an entrapped megakaryocyte (×400). **(D)** showed a Junkie pneumopathy, a foreign body giant cell with bone dust (long arrow). The surrounding lung tissue shows intraalveolar hemorrhages (dashed arrows) (×400).

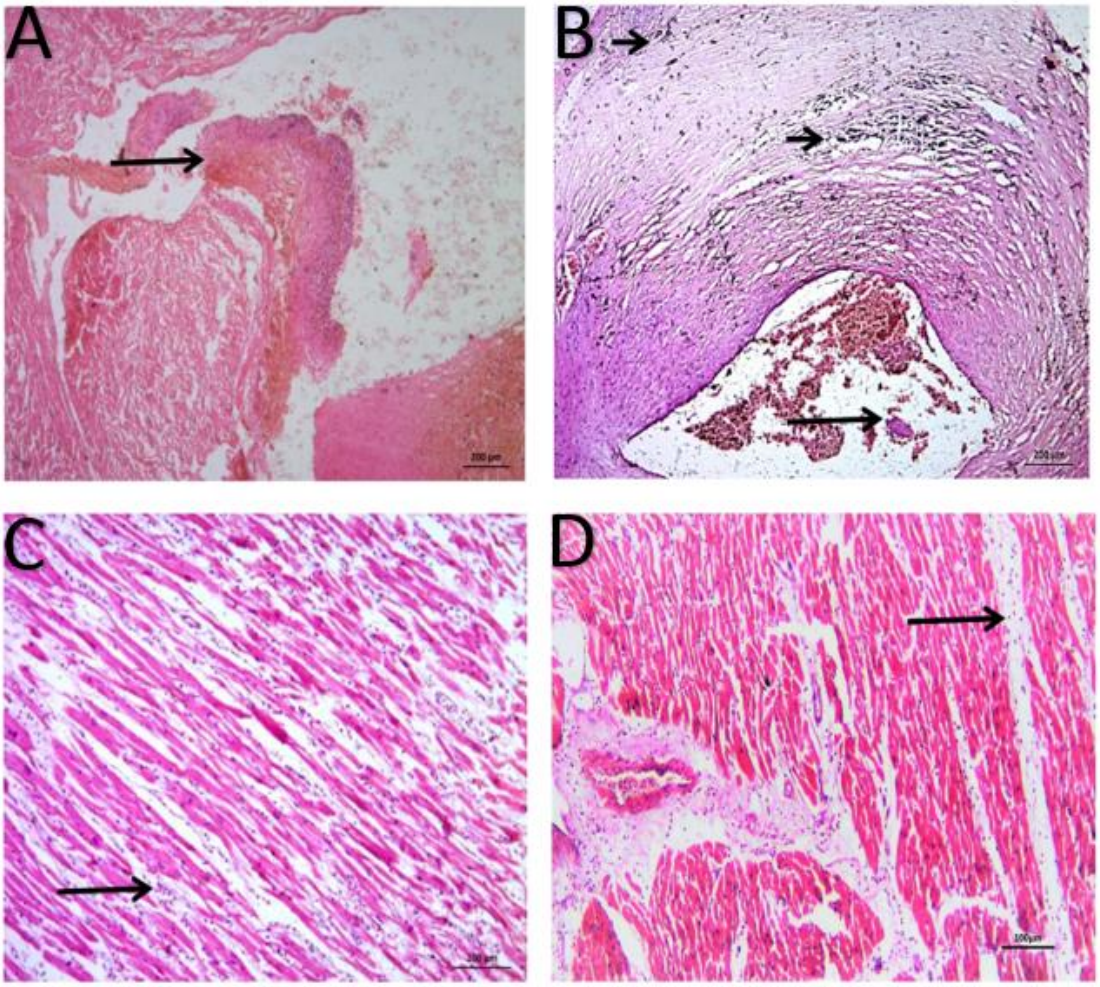

Figure (2): Photomicrograph of human heart tissue (Hx & E) stained sections (A) Heart mural thrombus, recent thrombus, luminal thrombus with lines of Zahn admixed with platelets and granulocytes (Long arrow) (×40). **(B)** Advanced coronary atherosclerosis with severe (>75%) occlusion, and dystrophic calcifications (short arrows), associated with early luminal thrombus with (Long arrow) (×40). **(C)** Neutrophilic myocarditis with moderate neutrophilic infiltrate (Long arrow) (×100). **(D)** Eosinophilic myocarditis with eosinophilic infiltrate (Long arrow) (×100).

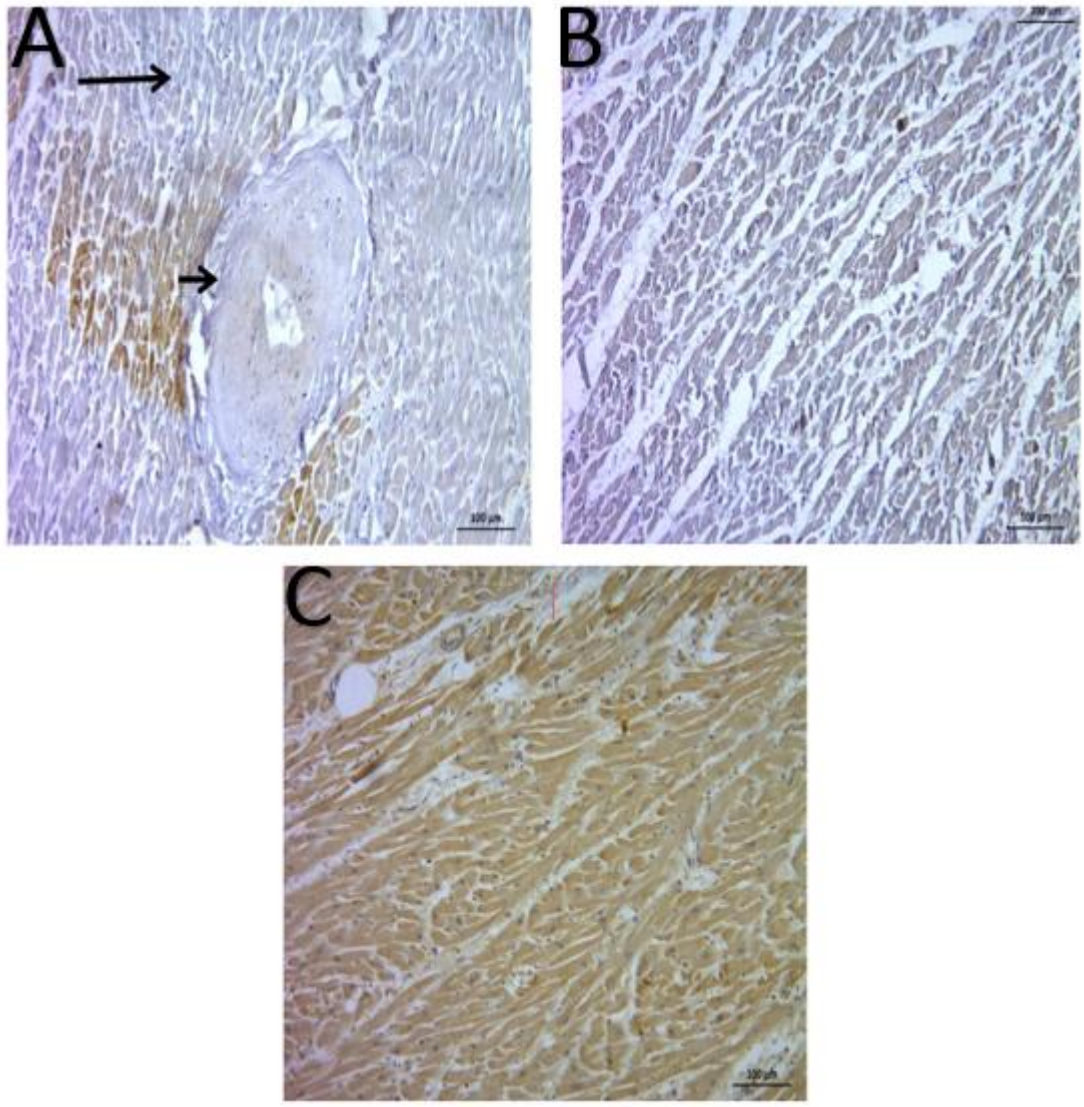

Figure (3): Photomicrograph of human cardiac tissue, immunohistochemical staining of the studied cases. (**A**) Troponin immunohistochemically stained slide, x100. Moderate troponin loss (-2), (long arrow). The coronary branch shows advanced arteriolosclerotic changes with thickened wall and marked luminal narrowing (short arrow), suggestive for AMI. (**B**) Myoglobin immunohistochemically stained slide, x100. Diffuse loss (-3), suggestive for AMI. (**C**) Caspase-3 immunohistochemically stained slide, x100. Diffuse strong positive reaction (+3), suggestive for AMI.

Discussion

The authors note that sudden and unexplained deaths present challenges for determining underlying causes in forensic pathology. While the majority have cardiovascular origins, there has been little research on non-cardiac contributions such as lung disease.

This study was a cohort retrospective analysis, that examined 80 autopsy cases of unexpected deaths in Egypt from 2009-2014. The results indicated that while 65% had various lung conditions, about 35% showed signs of acute lung injury (ALI). Additionally, 60% exhibited coronary artery disease and 40% had intrinsic heart muscle damage.

Sudden death of a young and healthy person is a devastating event for families. It gets media attention when it attacks athletes collapsing while performing routine training **(Oliva et al. 2011).**

The definition of the interval of a sudden death varies according to the institutions and authorities. The standard interval from onset of symptoms to cardiorespiratory cessation ranges from ½ to 24 hours. The World Health Organization defines it as death within 24 hours from the onset of symptoms, **(Saukko and Knight, 2004 and Burke, 2000).**

Topalov et al. (1999) have adopted the same definition. **Rosen (1998)** claims half an hour interval. **Berringer (2001), Faddis (2001)** and **De la Grandmaison and Durigon (2002)** have proposed a one-hour interval. **Kuller et al. (1966)** have a definition of 2-hours interval and **Basilico (1999)** has a definition 6-hours interval.

It was difficult and challenging to make a comparison between studies of autopsies of sudden death in adults because these studies may vary in their definition of sudden death, in their selection criteria of gender and age, and in the causes of death analyzed (limited to cardiac causes or not). There was a discrepancy between studies discussing general causes of sudden death (SD) and cardiac causes of sudden death. Articles discussing sudden cardiac death were the most studied entity, while studies dealing with other causes of sudden death were fewer **(Naneix et al., 2015).**

In the present study, an examination of the gender distribution among sudden unexpected/unexplained deaths revealed a notable prevalence of male cases, constituting 63.8% of the total, while females accounted for 37.3%. This observed gender discrepancy may be attributed to the heightened involvement of males in stressful events and strenuous muscular activities, coupled with a higher incidence of violence-related injuries among males.

This finding aligns with the cohort study conducted by **Sanchez et al. (2016),** encompassing 789 consecutive cases of sudden non-violent deaths. Their investigation reported 77.19% of cases as males and 22.81% as females, with males exhibiting a numerical predominance across all age groups. Similarly, **Soeiro et al. (2008)** observed a male predominance (67.4%) in their study of 218 autopsies on patients with acute respiratory failure (ARF) who died between 1990 and 2008 without a prior diagnosis of acute myocardial infarction (AMI)**.**

Moss and Mannino (2002) further support this trend through their analysis of age-adjusted annual Acute Respiratory Distress Syndrome (ARDS) mortality rates between 1979 and 1996. Their findings indicated consistently higher ARDS mortality rates among men compared to women**.**

In terms of the etiological cause of death, the current study identified sudden death as the predominant cause among males (84.2%), whereas females exhibited a

higher occurrence of surgical-related conditions and maternal mortality, constituting 52.2% and 100%, respectively. This distinction in etiological causes yielded a statistically significant difference between genders, emphasizing the association between gender and the primary cause of death. Notably, trauma to various body parts emerged as a prevalent cause of death among males, while maternal mortality played a dominant role in female fatalities.

This observation resonates with **Sessa et al. (2018),** who emphasized a greater risk of sudden death in males compared to females, a risk that amplifies with advancing age **(Islam et al., 2018).** Similarly, **Fnon et al. (2021)** reported significant gender-based disparities in the incidence of coronary atherosclerosis, with males representing 89.52% of cases and a male-to-female ratio of 9:1**.**

In the present study, a comprehensive examination of pulmonary histopathological changes unveiled notable findings in 95.0% of cases, with only 5.0% exhibiting lung congestion, considered as non-remarkable pathology in the lungs. The observed pulmonary histopathological changes were further classified into two distinct groups: The Acute Lung Injury (ALI) pathology group comprising 35.5% of cases and the group with other serious lung pathologies, excluding ALI, representing 64.5% of the total cases.

Within the ALI group, histopathological examination revealed distinctive findings. In 85.2% of cases, diffuse alveolar damage (DAD) was identified, while 11.1% exhibited DAD accompanied by eosinophilic lung disease, and 3.7% presented with end-stage interstitial lung disease.

Acute lung injury is characterized by the acute onset of severe respiratory distress following an identifiable injury, potentially arising from diverse etiologies such as sepsis, trauma, pneumonia, and drug toxicity. The condition is marked by severe oxygenation impairment, alveolar edema, and the eventual development of pulmonary hypertension. The most extreme manifestation of acute lung injury is recognized as Acute Respiratory Distress Syndrome (ARDS) **(Matthay et al. 2019).**

Clinically, ALI constitutes a significant cause of high morbidity and mortality, ranging from 10% to 90% among critically ill patients. Diagnosis is typically established by the acute onset of bilateral pulmonary infiltrates accompanied by hypoxemia, devoid of evidence indicating hydrostatic pulmonary edema **(Meyer et al. 2021).**

Matthay et al. (2019) elucidated that ALI or ARDS can arise from less common scenarios, including acute pancreatitis, transfusion-related acute lung injury (TRALI) following the transfusion of fresh frozen blood or its components, drug overdose, near drowning involving the inhalation of fresh or saltwater, and hemorrhagic shock.

Within the scope of this study, pathological findings within the heart were identified in a substantial 88.8% of cases, with 11.3% exhibiting no abnormalities upon examination with hematoxylin and eosin stain. The positive cardiac findings were further categorized into two principal groups: cardiac muscle pathology group and coronary pathology group.

Comprising 40.8% of cases, the cardiac muscle pathology group predominantly featured cases of ischemic heart disease (acute myocardial infarction), constituting 34.5% of this subgroup. A larger proportion, 59.2%, fell into the coronary pathology group, with a notable 57.1% of these cases exhibiting atherosclerosis, a condition intricately linked to ischemic heart disease.

This observed distribution aligns with prior research indicating that cardiovascular

causes stand as a predominant factor in sudden and unexpected deaths, often manifesting as a catastrophic complication of various cardiac conditions, frequently occurring without warning **(Saukko and Knight 2018).** Furthermore, **Naneix et al. (2015)** reported a concordant finding in their study on sudden adult death, where 66.1% of cases were attributed to cardiovascular causes.

Upon investigating the association between pulmonary histopathological changes (Acute Lung Injury [ALI] or other lung pathologies) and heart pathology (cardiac muscle pathology or coronary pathology) in the studied cases using hematoxylin and eosin (Hx&E) stain, no statistically significant difference was observed.

Detecting early myocardial ischemia poses challenges, as conventional tools, such as Magnetic Resonance Imaging (MRI) and transmission electron microscopy, are limited by high costs and an inability to diagnose specific reasons for mortality. Immunohistochemical methods, particularly the use of specific and sensitive markers like troponin (cTnT), myoglobin (MB), and caspase 3, offer insights into minimal myocardial damage, supporting the final diagnosis of Sudden Cardiac Death (SCD) **(Amin et al. 2015).**

Histological and immunohistochemical findings play a crucial role in confirming suspected diagnoses and suggesting differential diagnoses for various cardiac pathologies **(Bajwa et al. 2007).** In this study, the relationship between acute lung injury or other lung pathologies and acute myocardial infarction (AMI) or pathology was explored using specific cardiac markers.

Immunoreactivity of troponin (cTnT), myoglobin (MB), and caspase 3 was examined in 73 out of the total 80 cases. **Amin et al. (2015)** provided a classification system for detecting cardiac troponin and myoglobin staining depletion in cardiac muscle tissue. This system involved scoring the degree of staining loss on a scale from 0 to 3, where 0 indicates no loss, _1 signifies minimal decrease, _2 denotes clear decrease with some positivity remaining, and _3 indicates no positive (brown) staining. The scoring was based on the maximum loss noted in the examined area.

The intensity of staining for caspase 3 was also assessed and scored from 0 to 3 in areas with maximal expression.

In this study, troponin marker depletion exhibited a notable pattern, with marked loss observed in 23.3% of cases, moderate loss in 31.5%, focal loss in 23.3%, and no loss detected in 21.9% of cases. Similarly, myoglobin marker depletion displayed distinctive trends, with marked loss identified in 27.4% of cases, moderate loss in 31.5%, focal loss in 20.5%, and no loss observed in 20.5% of cases. The assessment of the caspase 3 marker revealed a diverse range of cytoplasmic reactions, including diffuse strong reactions in 34.2% of cases, moderately diffuse reactions in 32.9%, and focal positive reactions in the cytoplasm recorded in 32.9% of cases.

Further analysis delved into the relation between troponin depletion in cardiac muscle and specific ALI pathologies. A statistically significant difference emerged (p-value = 0.000), highlighting marked troponin loss in 91.7% of cases with diffuse alveolar damage (DAD) and 8.3% in cases with end-stage interstitial lung disease. Focal loss of troponin stain was recorded in 100% of cases with eosinophilic lung disease.

The study aligns with prior assertions by **Gerhardt et al. (1999),** emphasizing the nearly absolute myocardial tissue specificity and high sensitivity of cTnT**.** Recognized as a valuable diagnostic marker for acute myocardial cell damage, cTnT is elevated serologically within 4–6 hours following myocardial injury and stands as the current gold standard in myocardial infarction diagnosis **(Cina et al. 2001).** Results of

Arram et al. (2014) study claimed that the prognostic value of cardiac specific biomarkers, cardiac troponin in APE. Cardiac troponin was elevated in 45% of patients.

In cases of acute coronary syndrome, characterized by diffuse myocardial perfusion disturbance, histological examination and immunohistochemical markers illuminate findings or their absence across all myocardial areas. This substantiates the presumption of acute coronary insufficiency, offering valuable insights into the multifaceted nature of myocardial pathology **(Dettmeyer, 2018).**

Troponin and myoglobin markers emerge as reliable indicators of acute myocardial damage. A significant disparity in myoglobin immunoreactivity was evident between the Acute Lung Injury (ALI) group and the group with other pulmonary pathologies (p-value = 0.001). Myoglobin stain depletion was markedly lost in 48.1% of ALI cases, while focal depletion was observed in 32.6% of cases with other lung pathologies. Myoglobin, a sensitive indicator of muscle injury, serves as a valuable marker for determining infarction size, as noted in previous work **(Amin et al. 2015).**

Exploring the relationship between the level of myoglobin loss and pulmonary pathologic changes revealed a strong correlation (p-value = 0.001). Myoglobin depletion was notably lost in 72.2% of ALI cases, contrasting with focal loss in 93.3% of cases with other pulmonary pathologies.

Examining myoglobin depletion in cardiac muscle in the context of different ALI pathologies showed no statistically significant difference. This aligns with **Alzahrani et al. (2021)** assertion that myoglobin, considered a secondary cardiac and inflammatory biomarker, exhibited significantly higher levels in COVID-19 patients who did not survive**.** Pulmonary embolism cases demonstrated marked myoglobin loss in 40.0% of instances, no loss in 36.4%, and focal loss in 28.6%. **Arram et al. (2014)** highlighted the early elevation of serum myoglobin in 55% of patients with acute pulmonary embolism (APE).

A statistically significant difference emerged between the Acute Lung Injury (ALI) group and the group with other pulmonary pathologies concerning caspase 3 immunoreactivity (p-value = 0.016). In the ALI group, 51.9% of cases exhibited a diffuse strong cytoplasmic reaction, while 44.2% of cases with other lung pathologies displayed a focal positive cytoplasmic reaction.

Exploring the relationship between caspase 3 cytoplasmic reaction in cardiac muscle and ALI cases showed no statistically significant difference. DAD cases exhibited diffuse (92.9%), moderate (77.8%), and focal (75.0%) positive cytoplasmic reactions of caspase 3. The induction of inflammatory caspase 3s has been implicated in triggering inflammatory responses across various organ systems, including cardiovascular, brain, liver, and kidney injuries. Additionally, inflammasomes play a crucial role in pyroptosis, a process induced by inflammatory caspase 3s in acute lung injury. Research indicates slight variations in inducing factors and manifestations of pyroptosis among different cell types. In the bronchopneumonia group, caspase 3 stain exhibited a diffuse strong reaction in 40.0% of cases, focal positive cytoplasmic reaction in 31.6%, and moderate positive cytoplasmic reaction in junkie pneumopathy cases (35.7%)

Highlighting caspase 3 as one of the effector caspases directing cardiomyocyte apoptosis, **Dettmeyer (2018)** underscores its pivotal role as a key pathologic feature in heart failure. Caspase 3 may hold significance in patients with acute myocarditis and cases of dilated cardiomyopathy, suggesting its potential as a critical marker in unraveling the intricacies of cardiac pathology.

The outcomes of this retrospective study concluded that, there is an interconnection between acute lung and cardiac injury in

these sudden death cases that requires further investigation. Routine cardiac enzyme testing advised ALI patients to rule out cardiac involvement.

Limitation

Small sample size of 80 cases limits, lacked complete clinical history/details about patients, did not explore potential mechanisms linking ALI and AMI.

Future prospections

Larger multi-center prospective studies on sudden death exploring ALI-AMI linkage. Studies exploring pathological pathways interlinking lung and cardiac injury. Research cardiac enzyme patterns in ALI patients in clinical settings.

Evaluate cardiac status of ALI patients and vice versa for better management.

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التفاعلية المناعية للتروبونين والميوجلوبين والكاسبيز3 يظهر حدوث احتشاء عضلة القلب الحاد مصاحبا لإصابات الرئة الحادة في حالات الموت المفاجئ او غير المتوقع

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الملخص العربي

المقدمة: تشكل الوفيات المفاجئة وغير **المبررة سريريا** تحديات لأطباء الطب الشرعي لتحديد الأسباب الكامنة وراءها. وعلي الرغم من ان احتشاء عضله القلب يأتي على رأس الأسباب القلبية للوفيات غير المتوقعة والمفاجئة، الا أن القليل من الابحاث قد أُجريت حول الإصابات غير القلبية، مثل أمراض الرئة. من خلال هذه الدراسة تم عمل ربط لنتائج التشريح مع التقارير السريرية الواردة من المستشفى للتحقيق في الارتباط بين حدوث احتشاء عضله القلب مصاحبا لحالات اصابه الرئة الحادة هادفين بذلك تجنبا للأخطاء الطبية وما يترتب عليها من مسائلة قانونية قد يتعرض لها الاطباء.

طريقة البحث: تم العمل في هذه الدراسة على فحص قوالب من أنسجة القلب والرئة ميكروسكوبيا لحالات الموت مفاجئ غير المبرر لحالات مجهولة أرشيفياً لعدد 80 حالة تشريح والتي قد وردت الى مصلحة الطب الشرعي المصرية في الفترة بين يناير 2009 وديسمبر2014. تم عمل شرائح من مقاطع عينات من انسجه القلب **والرئة** وتم فحصها ميكروسكوبيا وتم إعادة تقييم التشخيص باستخدام صبغات الهيماتوكسلين والايوسين (Hx&E) الروتينية. تمت المساعدة في تشخيص واستبعاد حدوث احتشاء عضله القلب المبكر باستخدام صبغ العينات المختارة بالأجسام المضادة لـ التروبونين والميوجلوبين والكاسبيز 3 .

النتائج: أظهرت النتائج ان حوالي 35٪ من الحالات تظهر فيها علامات لإصابة الرئة الحادة ALI، بينما كانت نسبة 65٪ من الحالات تعاني من أمراض الرئة الإضافية بخلاف ALI، كما انه كان لدى حوالي 60٪ من الأشخاص مرض تصلب الشرايين التاجية بينما كان 40٪ يعانون من تلف في عضلة القلب.

وكانت من اهم نتائج هذا العمل انه لم يتم العثور على علاقة ذات دلالة إحصائية أو ارتباط بين حدوث احتشاء في عضلة القلب مع إصابات الرئة الحادة عند فحص الحالات باستخدام (Hx & E) بينما كانت هناك علاقة ذات دلالة إحصائية بينهم عندما تم فحص الحالات بواسطة دلالات الأنسجة القلبية المناعية.

الاستنتاج: تثير النتائج احتمالية ارتباط حدوث احتشاء في عضلة القلب مصاحبا لإصابات الرئة الحادة والذي يزيد بدوره من حدوث الوفيات المفاجئة أو غير المتوقعة. لذا يُنصح بإجراء اختبارات المناعة القلبية الروتينية لاستبعاد الإصابة القلبية للمرضى الذين يعانون من إصابة الرئة الحادة في العناية المركزة. كما ان هناك حاجة إلى المزيد من الدراسات حول العلاقات ذات دلالات احصائية وآليات الارتباط بين حدوث احتشاء عضلة القلب مع الإصابات الرئوية الحادة.

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