

Original Investigation

Multiple Organ Pathologies Underlying in Sudden Natural Deaths

Bora Ozdemir¹, Osman Celbis¹, Rezzan Onal², Bulent Mizrak³, Yunus Karakoc⁴

¹ Inonu University School of Medicine, Department of Forensic Medicine, Malatya, Turkey

² Pathology Department of State Hospital, Malatya, Turkey

³ Pathology Department of Damla Hospital, Elazig, Turkey

⁴ Inonu University School of Medicine, Department of Biophysics, Malatya, Turkey

Abstract

Aim of this study was to identify cause of death and related histological findings, and to find relationship between them in sudden natural deaths (SND) that were subjected to medicolegal autopsy. Totally 209 SND cases were enrolled in the study. After medicolegal autopsy, cause and manner of death were identified. A formula was formed to show the ratio of frequency of histological findings to cause of deaths in systems. By this formula, affected systems were compared. In SND cases, the ratio of extracardiac findings to extracardiac deaths was higher than that of cardiovascular findings to cardiovascular deaths (5.53 versus 2.00). We concluded that cardiovascular pathologies are still the most common in SND. The higher rate of extracardiac histological findings doesn't mean higher rate of SND due to extracardiac causes. Therefore, histological findings must be evaluated with great attention for preventing incorrect conclusions to identify causes of deaths in SND.

Keywords: sudden natural death, cause of death, histological findings, manner of death, sudden cardiac death, medicolegal autopsy, forensic medicine

Corresponding Address: Osman Celbis, M.D., Professor, Department of Forensic Medicine, Inonu University Faculty of Medicine, 44280 Malatya, Turkey.
E- mail: osmancelbis@gmail.com

Introduction

According to the World Health Organization definition of sudden death is of death within 24 hours from the onset of symptoms, but this time is too long for many clinicians and pathologists; some of them only accept death within one hour from the onset of illness. From a view point of forensic medicine, sudden natural death (SND) is mainly defined as rapid, unexpected and natural death. Although extracardiac causes may be involved in this process, it is assumed that causes of SND are mainly related to cardiovascular events. Most common definition of sudden cardiac death (SCD) is instantaneous cessation of cardiac output in individuals [1-6].

The main objective of a medicolegal autopsy is to determine cause and manner of death, and these autopsies help to reveal important data for public prosecutors. These autopsies may also be a valuable source for epidemiological information in addition to providing valuable information to the deceased's immediate family [7-11].

One of the challenges faced by the forensic pathologist is the inability to determine the cause of death in a person previously thought healthy. In a typical medical practice, approximately almost half of the deaths are natural, 5-10% are still unexplained after a gross autopsy, and 1-5% remain unclear (negative) after completion of the gross and histological examination and other laboratory tests [12]. The rate of SND of cardiac origin is approximately 50%, and the causes are mainly a function of age [13-15]. DiMaio [2] stated that the ratio of deaths due to cardiovascular disorders were 42%. The most common cause of SND is connected to cardiovascular system and in turn followed by respiratory, cerebrovascular and, digestive and urogenital systems.

It was reported that concordance between clinical and pathological causes of death are moderate, and the autopsy still provides a very important procedure for evaluating causes of deaths. In a prospective study, disagreements occurred in cases with pathological causes of death as circulatory/cardiac diseases [16]. Over one fifth of clinically unexpected autopsy findings can be correctly diagnosed only by histological examination. Autopsy and particularly autopsy histology are still the most accurate method of determining the cause of death and auditing accuracy of clinical diagnosis, diagnostic tests and death certification [17]. However, autopsy findings and clinical examinations may not be enough to evaluate accurate

and consistent diagnosis and reporting of the cause of death. Sudden adult deaths may remain sometimes as an enigma after a complete autopsy [5].

The circumstances strongly suggesting a cardiac cause for SND may emerge problems for the forensic pathologist. Ischemic heart disease (coronary atherosclerosis) is undoubtedly the most frequent cause but even when this is so the detailed pathology is controversial [17,18].

Aim of this study was to identify cause of death and related multiple histological organ findings and to find the relationship between them in SND cases that were subjected to medicolegal autopsy.

Materials and methods

After approved of our study protocol by local Ethics Committee, we had reviewed retrospectively the files of medicolegal autopsies which were performed in the Morgue Department of the Malatya Branch of the Council of Forensic Medicine and pathology departments of Inonu University School of Medicine. Autopsy files within eight years were evaluated and enrolled in our study.

For the histological examinations, tissue samples were taken from five different main organs (brain, heart, lung, liver and kidney) of each corpse. Hematoxylin-eosin stained sections of organs were evaluated. Toxicological analyses were also performed for all cases and occasionally microbiological studies were performed when needed.

After medicolegal autopsy, cause and manner of death had been identified by evaluating all data achieved from autopsy findings including histological examination, in addition to scene investigation and circumstances of death, clinical information and laboratory findings. Having completed all investigations, the subjects of whom the manners of death were assessed as SND were identified. The cases of homicides, suicides, accidental deaths, intoxications were excluded, as well as the cases that were initially informed as SND, but exact causes were changed after medicolegal autopsy. Thereby, totally 209 adult SND (over 15 years) among the 2189 cases were enrolled in our study.

Age and gender distribution, frequencies of histological findings, causes of deaths and number of histological findings according to body systems were presented in the tables. From these numerical data, it was formed a formula that shows the ratio of frequency of histological

findings to death of causes in body systems. By using this formula, affected body systems were compared among themselves.

Results

In our study group 209 SND cases were consisted of 153 males and 56 females. The average age was 47.1 years (in males 47.3; in females 46.8). The bulk of our series was consisted of the cases aged between 30-70 years old. There was a remarkable male dominance (73% male, 27% female) (Table 1). It was obtained totally 754 histological findings on tissue specimens which were taken from main organs of each corpse in 209 cases.

Table 1. Age and gender distribution of SND cases

Age	Male (Mean: 47.3)		Female (Mean: 46.8)		Total (Mean: 47.1)	
	n	%	n	%	n	%
15-20	11	5.2	4	1.9	15	7.1
21-30	18	8.5	9	4.3	27	7.1
31-40	26	12.4	11	5.3	37	17.7
41-50	31	14.7	10	4.8	41	19.5
51-60	32	15.2	4	1.9	36	17.1
61-70	20	9.5	10	4.8	30	14.3
71-80	12	5.7	8	3.8	20	9.5
81-90	3	1.5	0	0	3	1.5
Total	153	73	56	27	209	100

As indicated in the Table 2 cardiovascular findings were the most common in histological findings covering mainly atherosclerosis, myocardial infarct, and myocardial hypertrophy, which were 30.2% (n= 228/754) of our series. In addition, there were different kinds of lesions, including coronary artery thrombosis, myocarditis, arrhythmogenic right ventricular cardiomyopathy, aortic dissection, bridging of coronary arteries and atrial myxoma.

Table 2. Frequencies of histological organ findings in SND.

Organs	Histological findings	N	%
Cardiac findings	Atherosclerosis	96	42.1
	Myocardial infarct	61	26.8
	Myocardial hypertrophy	39	17.1
	Coronary thrombosis	11	4.8
	Myocarditis	7	3.1
	Arrhythmogenic right vent. cardiomyopathy	5	2.1
	Aortic dissection	4	1.8
	Bridging of coronary arteries	4	1.8
	Atrial myxoma	1	0.4
	Cardiac Total	228	100
Pulmonary findings	Edema	80	42.5
	Intraalveolar hemorrhage	54	28.7
	Emphysema	21	11.2
	Pneumonia	15	8.0
	Pulmonary hypertension	6	3.2
	Foreign body aspiration	5	2.7
	Bronchiolitis	5	2.7
	Embolus	2	1.0
	Pulmonary Total	188	100
Cerebral findings	Edema	46	40.0
	Ischemic neurons	35	30.4
	Subarachnoidal hemorrhage	24	20.9
	Intraparenchymal hemorrhage	8	7.0
	Basilar artery sclerosis	2	1.7
	Cerebrovascular Total	115	100
Kidney findings	Chronic pyelonephritis	32	40.5
	Simple cyst	15	19.0
	Acute tubular necrosis	10	12.7
	Urolithiasis	9	11.4
	Hemorrhage	6	7.6
	Proteinuria	4	5.0
	Renal cell cancer	2	2.5
	Amyloidosis	1	1.3
	Kidney Total	79	100
Liver findings	Isolated hepatocyte necrosis	47	35.6
	Steatosis	42	31.9
	Chronic hepatitis	31	23.5
	Cavernous hemangioma	4	3.0
	Precirrhotic changes	4	3.0
	Cirrhosis	2	1.5
	Granulomatous inflammation	2	1.5
	Liver Total	132	100
Total		754	100

Common findings in pulmonary system were mainly edema, intraalveolar hemorrhage, emphysema and pneumonia. Different kinds of lesions including foreign body aspiration, bronchiolitis, pulmonary hypertension and embolus were also encountered.

Edema, ischemic neurons and subarachnoid or intraparenchymal hemorrhage were prominent lesions among the cerebrovascular system findings whereas the frequency of basilar artery sclerosis was lower.

When assessed kidney findings, there were found mainly chronic pyelonephritis, simple cyst, acute tubular necrosis and urolithiasis. Hemorrhage, proteinuria, renal cell cancer, amyloidosis were also available. These findings were not the possible causes of sudden deaths, but they are the common kidney findings in renal diseases.

Among the liver pathologies, most frequent findings were isolated hepatocyte necrosis, steatosis and chronic hepatitis. Additionally, cavernous hemangioma, precirrhotic changes, cirrhosis and granulomatous inflammation were also detected at lower frequency (Table 2).

When viewing organ findings and causes of death in the table 3, the most common cause of SND was cardiovascular disorder. The ratio of cardiovascular disorders among the total sudden death causes was found 54.5% (114/209) and, followed by pulmonary diseases and cerebrovascular diseases at the ratio of 22.4% and 10.5%, respectively. The other ratios of SND causes and organ findings were also presented in the Table 3.

Table 3. Number and frequency of histological findings and cause of death according to body systems

Body Systems	Histological Findings		Cause of Death	
	n	%	n	%
Cardiovascular	228	30.2	114	54.5
Pulmonary	188	24.9	47	22.4
Cerebrovascular	115	15.3	22	10.5
Urogenital	79	10.5	6	2.9
Digestive	132	17.5	5	2.4
Other	12	1.6	15	7.1
Total	754	100	209	100

From our results, we assessed that the ratio of extracardiac findings to extracardiac deaths was higher than that of cardiovascular findings to cardiovascular deaths. For our series these ratios were found 5.53 and 2.00, respectively.

$$\frac{\text{extracardiac findings}}{\text{extracardiac deaths}} = \frac{526}{95} = 5.53$$

$$\frac{\text{cardiovascular findings}}{\text{cardiovascular deaths}} = \frac{228}{114} = 2.00$$

$$5.53 \gg 2.00$$

As mentioned below, these outputs were presented by a formula in order to explain the results of our series.

$$\frac{\text{extracardiac findings}}{\text{extracardiac deaths}} > \frac{\text{cardiovascular findings}}{\text{cardiovascular deaths}}$$

Discussion

Investigations in the cases of SND take an important place in forensic practice. Medical examiners are often confronted with normal deaths of subjects without any prior medical history and found dead under apparently natural circumstances. However, even a complete autopsy including toxicological analyses, some of them remain unexplained in practice [19].

In previous studies, it was reported that the ante mortem diagnosis had been changed in some cases after autopsy [16,17,20]. Most studies show an unsatisfactory agreement between the clinical diagnosis and the autopsy diagnosis. In a study it was concluded that the rate of initial death certificate accuracy is only one half in a group of SND after performing autopsies [21]. SND have been occurred because of many causes. In medicolegal autopsies, SND have the first or second order in most series [1,11,22-24]. In our series, there were total 2189 medicolegal autopsies, and SND were encountered in 209 cases. SND were the second order after accidental deaths in our series. Our results show that SND causes are greatly similar to those of some other series [5,25].

In the Worldwide, SND emerge dominantly in males (26). Most common causes of SND are cardiovascular, pulmonary, cerebral, urogenital and digestive diseases in decreasing order [2,27]. In previous series, rate of cardiovascular diseases was reported between 40% to 84% [5,13,26,28-31]. Our results were similar to previous articles in that cardiovascular pathologies was the most common cause for SND, and frequency of cardiovascular causes for SND was found 54.5 %.

It was previously reported that more than half of the hearts were found structurally normal in non-atherosclerotic cardiac deaths in a population aged over 15 years. From their result, it was concluded that the concept of the structurally normal heart in sudden death and the need for histological examination to detect underlying disease is highlighted [32].

In the literature, the true incidence of sudden cardiac deaths remains unclear, with a wide range in available estimates [33]. Among the cardiovascular pathologies, ischemic heart disease is the most common cause for SND [1-4]. Coronary atherosclerosis and acquired forms of cardiomyopathy are the most common findings at autopsies of sudden cardiac death in adults [14,15]. Coronary atherosclerosis was also seen highly in 42.1% (96/228 cases) of our series. Recent and/or old myocardial infarcts were present in 26.8% (61/228 cases) of cases. Our series had 17.1% (39/228 cases) with myocardial hypertrophy, appearing mainly in hypertension. This can be explained by the higher age group of our cases and high occurrence of hypertension in our population. Epidemiological and autopsy studies suggest a close link between aging and the clinical manifestation of atherosclerosis [34]. We found rate of coronary thrombosis as 4.8% (11/228) which was lower than previous studies [14,15]. Rate of myocarditis have also extreme variations in the literature [4,11], and its ratio was 3.1% (7/228) in our population.

Arrhythmogenic right ventricular cardiomyopathy was found in 2.1% (5/228 findings, 5/209 cases), aortic dissection and bridging of coronary arteries, each one was found in four cases (4/228). These pathologies are rare and, some of sudden unexplained deaths may be related to these pathologies [2,35]. Among the cardiovascular disorders, aortic dissection was reported in 1.3% of cases by Escoffrey and Shirley [11]. Puranik et al. [26] also recorded the ratio of cardiac deaths due to aortic dissection as 5%. Aortic dissection were found in 1.8% (4/228 findings, 4/209 cases) of our series. Additionally, we diagnosed atrial myxoma in only one case of our series.

In our study, most common pulmonary finding was intraalveolar edema as 42.5% (80/188). It may appear as a complication in various situations such as congestive heart failure, smoke inhalation, tuberculosis, anaphylactic reactions, etc [36,37]. On the other hand, pulmonary histopathologic findings were intraalveolar hemorrhage (28.7%), emphysema (11.2%), pneumonia (8.0%), bronchiolitis (2.7%), pulmonary hypertension (3.2%), and foreign body aspiration (2.7%). Pulmonary embolus was seen in 1.0%. In previously studied series, pulmonary embolus rate was mentioned as 3.4-12.5% [26,29,31]. But, we found pulmonary embolus rate lower than previous studies.

Among the cerebrovascular disorders, subarachnoid hemorrhage and intracerebral hemorrhage are important causes of unexpected death often between the ages of 40-70 years [24]. In our series, 10.5% (22/209 cases) of deaths were related to cerebrovascular diseases. In the literature, deaths due to cerebrovascular diseases ranged between 8.7-24.1% [2,11,27,31]. In central nervous system, ischemic red neuron was our most prominent finding with 30.4% (35/115) frequency. The high percentage of this finding may be explained by its occurrence in different death situations such as cardiovascular, cerebrovascular and pulmonary failure. Cerebral edema was seen in 40% (46/115) of cases, and former explanation is also valid for this entity.

In liver, isolated hepatocyte necrosis was seen in 35.6% (47/132) of cases. This high percentage is striking among the findings. Isolated hepatocyte necrosis is associated with hepatitis, drug and alcohol abuse, toxications etc [38,39]. Chronic hepatitis was 23% in liver lesions as a high occurrence in our population, and it can be easily said that hepatitis is also major public health problem for our population. Steatosis was present in 42 cases, but this is not an important histopathologic finding, occurs in obesity, hepatitis, alcoholism etc. and it is reversible. Our liver results were similar with the previous studies [2,3,40].

As a regard of kidney findings, chronic pyelonephritis was most frequent (40.5%, 32/79) of kidney lesions, and this finding may also be assessed as a threat for public health in this population, because it culminates in renal insufficiency if persists [41]. Acute tubular necrosis (ATN) was found in 10.7% of kidney lesions. It is the most common cause of intrinsic acute renal failure and usually occurs after an acute ischemic or toxic event [42]. We can say that simple cysts are seen in old ages, and they have no clinical importance. Every

one of 10 histological examinations (79/754) showed the urogenital system pathologies. But, number of SND due to urogenital disorders was found lower than this ratio (6/209).

SCD is considered as occurring in structurally normal heart when a thorough gross and histological examination fails to detect any plausible organic substrate accounting for cardiac arrest. Noteworthy, it was reported that macroscopic heart features were normal in nearly one third of young SCD victims. However, histological studies may not be enough to determine concealed pathological substrates such as focal myocarditis or cardiomyopathy and conduction system diseases in some cases and the mechanism of their SCD remained unexplained [43].

The heart can be found grossly and histologically normal in a not-so-minor amount of cases (the so-called unexplained SD) and inherited ion channel diseases are implicated (long and short QT syndromes, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia). Postmortem investigation may still represent the first opportunity to make the proper diagnosis also in the setting of a structurally normal heart and the employment of molecular techniques [44].

Total number of organ findings was higher than total number of deaths, because there were many or multiple organ findings in all SND cases. Every SND is almost related to one or more histological organ findings (209/754). For example, the cases that died due to cardiovascular disorders had two histological findings on average (114/228). When viewing the other organ findings, there were much more extracardiac histological organ findings in each SND case. In fact, digestive system findings were found higher than the number of digestive system-related SND (132/5). In other words, only one of every 7 histological findings (132/754) was related to digestive system pathologies, whereas SND due to digestive system was infrequent.

Since heart is one of the 5 main organs, it can be predicted that 20% of histological findings should be related to cardiac events. However, the cardiac histological findings were available in 30.2% of cases (228/754). On the other hand, cardiac causes in all SND were 54.5% (114/209). This level is higher than expected. From these findings, we may think that if any cardiac or extracardiac disorder affects the cardiovascular system, it can generate more than

one histological change in heart. Additionally, higher average age of our series may be another reason for emerging of frequent cardiovascular pathologies.

By using our formula as mentioned above, the ratios of findings to death causes were calculated as 4.0, 5.2, 13.2, and 26.4 for pulmonary, cerebrovascular, urogenital, and digestive systems, respectively. This ratio shows that there are various histopathological findings in SND and the ratio of histological findings underlying in cardiac and extracardiac SND are different.

Although the most frequent cause of death was related to cardiovascular pathologies in SND cases, number of histological findings were higher in cases of whose the cause of deaths were extracardiac. In medicolegal autopsies, especially for SND, we propose that every possible organ must be sampled for histological examination, and must be evaluated with a multidisciplinary approach (scene investigation, medical history, biochemical, microbiological, toxicological, etc.). Thereby, cause of death can be accurately determined in SND cases.

Key points

- In sudden natural deaths, cause of death can only be determined by autopsy.
- Cardiac disorders are most common causes of sudden natural deaths.
- It is difficult to determine cardiac electrophysiological disorders in sudden natural deaths.
- In cardiovascular system related natural deaths, number of cardiac histological findings is lower than those of other body systems.
- It is crucial that innovative techniques should be used to determine causes of death exactly.

Conclusion

We concluded that cardiovascular diseases are still the most common in SND as previously reported. When calculated by our formula, the ratio of extracardiac histological organ findings to the extracardiac deaths is higher when compared to those of cardiovascular system in SND cases. Although this result is to be noteworthy, the higher rate of extracardiac histological organ findings does not mean the higher rate of SND due to extracardiac causes.

Therefore, while determining the cause of death; histological organ findings must be evaluated with great attention in order to prevent the incorrect conclusions to identify causes of deaths in SND cases. Finally, exact cause of SND cannot be determined by using routine autopsy procedures and needs further investigations. Less amounts of cardiac findings in SND cases may be attributed to undetermined gross and microscopic evaluations. Hence, the frequency of cardiac findings is lower than expected.

References

1. Saukko P, Knight B. *Knight's forensic pathology*. 3rd ed. London: Arnold; 2004.
2. DiMaio WJ, DiMaio D. *Forensic pathology*. 2nd ed. London, New York, Washington: CRC Press; 2001.
3. Simpson K, Knight B. *Forensic medicine*. 11th ed. London: Hodder Arnold Publication; 1997.
4. Soysal Z, Eke SM, Çakd r AS. *Adli otopsi (in Turkish)*. Istanbul: Istanbul Universitesi Cerrahpasa Tıp Fakultesi Yayinlari; 1999.
5. de la Grandmaison GL, Durigon M. Sudden adult death: a medico-legal series of 77 cases between 1995 and 2000. *Med Sci Law*. 2002;42(3):225-32.
6. Spooner PM, Priori SG, Myerburg RJ. Spotlight on sudden cardiac death. *Cardiovasc Res*. 2001;50(2): 173-6.
7. Chen K. The coroner's necropsy: an epidemiological treasure trove. *J Clin Pathol*. 1996;49(9):698-9.
8. O'Sullivan JP. The coroner's necropsy in sudden death: an under-used source of epidemiological information. *J Clin Pathol*. 1996;49(9):737-40.
9. Nemetz PN, Ludwig J, Kurland LT. Assessing the autopsy. *Am J Pathol*. 1987;128(2):362-79.
10. Escoffery CT, Shirley SE. Autopsy rates at the University hospital of the West Indies, 1968-1997. *West Indian Med J*. 2000;49(2):164-8.
11. Escoffery CT, Shirley SE. Causes of sudden natural death in Jamaica: a medicolegal (coroner's) autopsy study from the University Hospital of the West Indies. *Forensic Sci Int*. 2002;129(2):116-21.
12. Cohle SD, Sampson BA. The negative autopsy: Sudden cardiac death or other? *Cardiovasc Pathol*. 2001;10(5):219-22.
13. Fragkouli K, Vougiouklakis T. Sudden cardiac death: an 11-year postmortem analysis in the region of Epirus, Greece. *Pathol Res Pract*. 2010;206(10):690-4.
14. Virmani R, Burke AP, Farb A. Sudden cardiac death. *Cardiovasc Pathol*. 2001;10(5):211-8.
15. Virmani R, Burke AP, Farb A. Sudden cardiac death. *Cardiovasc Pathol*. 2001;10(6):275-82.
16. Pinto Carvalho FL, Cordeiro JA, Cury PM. Clinical and pathological disagreement upon the cause of death in a teaching hospital: analysis of 100 autopsy cases in a prospective study. *Pathol Int*. 2008;58(9):568-71.
17. Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review. *Histopathology*. 2005;47(6):551-9.
18. Davies MJ, Popple A. Sudden unexpected cardiac death: a practical approach to the forensic problem. *Histopathology*. 1979;3(4):255-77.

19. Michaud K, Romain N, Taroni F, Horisberger B, Mangin P. Evaluation of a simplified method of the conduction system analysis in 110 forensic cases. *Forensic Sci Int.* 2002;130(1):13-24.
20. Yayci N, Uzun I, Arslan M, Iris M. The Value of the autopsy in the case of postoperative deaths with suspicion of malpractice (in Turkish). *Turkiye Klinikleri J Foren Med.* 2004;1(2):57-61.
21. Tavora F, Crowder C, Kutys R, Burke A. Discrepancies in initial death certificate diagnoses in sudden unexpected out-of-hospital deaths: the role of cardiovascular autopsy. *Cardiovasc Pathol.* 2008;17(3):178-82.
22. Ramu M. A 3 year review of medicolegal autopsies performed at the Kingston Public Hospital, Jamaica (1973-1975). *West Indian Med J.* 1976;25(4):235-40.
23. Hirsch CS. Forensic pathology and the autopsy. *Arch Pathol Lab Med.* 1984;108(6):484-9.
24. Amakiri CNT, Akang EEU, Aghadiuno PU, Odesanmi WO. A prospective study of coroner's autopsies in University College Hospital, Ibadan, Nigeria. *Med Sci Law.* 1997;37(1):69-75.
25. Salacin S. An analysis of the medicolegal autopsies performed in Adana, Turkey, in 1983-1988. *Am J Forensic Med Pathol.* 1991;12(3):191-3.
26. Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. *Heart Rhythm.* 2005;2(12):1277-82.
27. Di Maio VJ, Di Maio DJ. Natural death as viewed by the medical examiner: a review of 1000 consecutive autopsies of individuals dying of natural disease. *J Forensic Sci.* 1991;36(1):17-24.
28. Murai T, Baba M, Ro A, Murai N, Matsuo Y, Takada A, Saito K. Sudden death due to cardiovascular disorders: a review of the studies on the medico-legal cases in Tokyo. *Keio J Med.* 2001;50(3):175-81.
29. Manfredini R, Portaluppi F, Grandi E, Fersini C, Gallerani M. Out-of-hospital sudden death referring to an emergency department. *J Clin Epidemiol.* 1996;49(8):865-8.
30. Loire R, Tabib A. Unexpected sudden cardiac death. An evaluation of 1000 autopsies. *Arch Mal Coeur Vaiss.* 1996;89(1):13-8.
31. Vanbrabant P, Dhondt E, Sabbe M. What do we know about patients dying in the emergency department? *Resuscitation.* 2004;60(2):163-70.
32. Fabre A, Sheppard MN. Sudden adult death syndrome and other non-ischaemic causes of sudden cardiac death. *Hearth.* 2006;92(3):316-20.
33. Kong MH, Fonarow GC, Peterson ED, Curtis AB, Hernandez AF, Sanders GD, Thomas KL, Hayes DL, Al-Khatib SM. Systematic review of the incidence of sudden cardiac death in the United States. *J Am Coll Cardiol.* 2011;15;57(7):794-801.
34. Orlandi A, Bochaton Piallat ML, Gabbiani G, Spagnoli LG. Aging, smooth muscle cells and vascular pathobiology: implications for atherosclerosis. *Atherosclerosis.* 2006;188(2):221-30.
35. Celbis O, Aydin NE, Mizrak B, Ozdemir B. Arrhythmogenic right ventricular dysplasia cases in forensic autopsies. *Am J Forensic Med Pathol.* 2007;28(3):235-7.
36. Celbis O, Aydin NE, Usta U, Selcuk MA. Hemoptysis due to pulmonary tuberculosis causing sudden death. *JJUMF.* 2004;11(4): 251-3.
37. Yilmaz R, Yuksekbaz O, Erkol Z, Bulut ER, Arslan MN. Postmortem findings after anaphylactic reactions to drugs in Turkey. *Am J Forensic Med Pathol.* 2009;30(4):346-9.
38. Roschlau G. Drug-induced liver damage from the morphologic viewpoint [Article in German]. *Gastroenterol J.* 1990;50(1):6-11.
39. Hoek JB, Pastorino JG. Cellular signaling mechanisms in alcohol-induced liver damage. *Semin Liver Dis.* 2004;24(3):257-72.
40. Usta U, Mizrak B, Celbis O. Evaluation of the incidence of HBsAg and HBeAg expressions by immunohistochemically in adult forensic autopsy livers. *Turkish Bulletin of Pathology.* 2002;19(2):63-5.

41. Kunin CM. Does kidney infection cause renal failure? *Annu Rev Med.* 1985;36:165-76.
42. Cheung CM, Ponnusamy A, Anderton JG. Management of acute renal failure in the elderly patient: a clinician's guide. *Drugs Aging.* 2008;25(6):455-76.
43. Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. *Cardiovasc Res.* 2001;50(2):399-408.
44. Basso C, Carturan E, Pilichou K, Rizzo S, Corrado D, Thiene G. Sudden cardiac death with normal heart: molecular autopsy. *Cardiovasc Pathol.* 2010;19(6):321-5.