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Rhabdomyolysis in drug-related deaths

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Abstract

Background: This study aims to detect myoglobin staining in the cases in which were suspected that intoxication was the cause of death.

Materials and method: This study selected the drug-related death cases including those with toxic blood levels of substances. These drug-related death cases were classified into two groups: (1) suggestive of intoxication death group and (2) other causes of death group which was control group. The kidneys of all these cases were immunohistochemically stained with the myoglobin antibody for rhabdomyolysis diagnosis.

Results: There were 50 drug-related deaths separated into 28 study cases and 22 control cases. The positive myoglobin stain was found in 17 cases (60.7%) in the study group and 5 cases (22.7%) in the control group. The difference between two groups was statistically significant ($p = 0.007$).

Conclusions: Myoglobin detection in kidney by immunohistochemistry should be done to help for confirming the cause of deaths in these drug-related death cases.

Keywords: Forensic toxicology, Rhabdomyolysis, Myoglobin, Immunohistochemistry

Background

Nowadays, intoxication, one of the world's major problems, is a common cause of death in unnatural fatality cases, which have been autopsied. Moreover, according to the World Drug Report (2016), over 29 million people were estimated to suffer from drug use disorders (United Nations Office on Drugs and Crime, 2016).

To certify the cause of death, in principle, forensic pathologists need to apply three main factors: the autopsy findings, the toxicology results, and finally, the history and circumstance of death (Gil, 2017; Dimaio & Dimaio, 2001).

However, forensic pathologists conclude that death from intoxication is very difficult. This is because drug and intoxication deaths are largely functional, and there are few definitive gross or microscopic findings at the autopsy to confirm the diagnosis (Gil, 2017). Furthermore, the level of drugs found in the postmortem is mostly not in a fatal range but displays a toxic level. In addition, although toxic or fatal, it may not be interpreted because of the redistribution mechanism (Yarema & Becker, 2005). Also, the history and circumstance of death are not always reliable, as sometimes the people who overdose do not die immediately after taking the drug and were sent to a hospital until death with no history. Consequently, a forensic pathologist sometimes did not know drug use history. Therefore, it may be necessary to find another specific factor to prove the cause of death, which is drug-induced rhabdomyolysis.

Rhabdomyolysis can be divided into two groups: traumatic and non-traumatic. "Drug-induced rhabdomyolysis" is therefore the most common cause in non-traumatic rhabdomyolysis (Miller, 2017).

Alcohol and illicit drug consumption can cause direct and secondary effects to the skeletal system from the destruction of the skeletal muscle cells (Hohenegger, 2012; Coco & Klasner, 2004). Rhabdomyolysis leads to an increase in the serum creatinine kinase (CK) level to a life-threatening condition associated with an extreme exacerbation in the CK level and electrolyte imbalances resulting in death from acute renal failure (Hohenegger, 2012; Torres et al., 2015).

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A diagnosis of rhabdomyolysis in patients was conducted by laboratory tests including serum CK and urine myoglobin (Miller, 2017; Torres et al., 2015). Serum CK may have resulted from the incidental findings in a patient without muscle-related symptoms or with only minimal nonspecific muscular symptoms (Torres et al., 2015; Efstratiadis et al., 2007) together with the postmortem. Therefore, serum CK detection is not specific and may not be considered as appropriate evidence (Spitz & Spitz, 2006). Myoglobin is a heme protein in the skeletal muscle when skeletal injuries develop. Then, myoglobin will appear in the bloodstream then pass into the kidney and excrete into the urine (Zutt et al., 2014; Moghadam-Kia et al., 2016; Ishigami et al., 2003). However, with the limitations of urine collection in corpses, detection of urinary myoglobin is not always available for all cases. Detection of myoglobin casts deposited in the kidney tissue by hematoxilin and eosin can prove the existence of rhabdomyolysis. Nevertheless, "the morphology of the myoglobin casts ranged from light, almost translucent and refractile, to pink, to dark red and slightly brown granular casts" (Liapis et al., 2016). Using a myoglobin antibody by applying an immunohistochemistry method would be more specific and advantageous, as it would be a more appropriate way to confirm rhabdomyolysis. One previous study about the detection of rhabdomyolysis was conducted using this approach (Welte et al., 2004).

To assist forensic pathologists certify intoxication as the cause of death, this research study selected the detection of myoglobin staining in order to diagnose rhabdomyolysis by applying immunohistochemistry in the cases in which it was suspected that intoxication was the cause of death, but there were no other specific findings. In addition, the results of this study may encourage physicians to be further aware of this condition in their patients.

Materials and methods

This study was carried out in the Forensic Medicine Division, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand. During the years 2015 and 2016, 884 medicolegal autopsy cases were investigated. Toxicological investigations were done depending on the decisions of the pathologists. The postmortem blood from the femoral vessels was collected in tubes with sodium fluoride preservative and kept in a refrigerator (4 °C) before sending to the toxicology laboratory in Ramathibodi Hospital, which has ISO/IEC 17025:2005 certification. Two analyses were done in the laboratory. Firstly, screenings for drugs and drugs of abuse were carried out using Liquid Chromatography (Bruker)-Quadrupole Time-of-Flight Mass Spectrometry (Dionex Ultimate 3000). The limit of detection was 0.001–0.1 mg/L depending on the type of drug. The laboratory was able to detect more than 1600 drugs and compounds. The list of drugs and drug groups is shown in Table 1. If a significant drug was detected, drug quantitation was done. The drug quantitative analysis was undertaken by using liquid chromatography-mass spectrometry/mass spectrometry. Secondly, blood alcohol concentrations (BAC) were measured by using Agilent technologies 7890 B Headspace gas chromatography/flame ionisation detector. Ethanol determination was performed using linear calibration with 10, 20, 50, 100, 200, 300, 400, and 500 mg% of aqueous ethanol solutions and isopropanol as an internal standard. The lower limit of quantitation was the lowest calibrator concentration (10 mg%).

This study selected the drug-related death cases including those with toxic blood levels of substances that were detected or those found with multiple drugs. The toxic levels of common substances are shown in Table 2 (Schulz et al., 2012; Winek et al., 2001). Ethanol toxic level in this study means that ethanol is the cause of obvious intoxication with nausea or a staggering gait. Moreover, this level is legal intoxication for driving in many countries.

If there were inappropriate paraffin-embedded sections of the kidneys, the cases were excluded. The other important exclusion criteria were admission to hospital, history of infection, history of exertional activity, and decomposition. Finally, 50 drug-related death cases were studied.

The demographic data and history of these cases were recorded, which included the circumstances of death, history of alcohol consumption, history of drug abuse, gender, and age. Furthermore, the weight of the internal organs: heart, both lungs, brain, and liver was also collected.

The paraffin-embedded tissue of the kidneys, which were already stained with hematoxilin eosin, was immunohistochemically stained with a myoglobin antibody. The polyclonal antibody with a specific affinity to human

Table 1 The list of drugs and types of drugs that was screened

Amphetamine-like	Cocaine
Analgesics (non-opioids)	Diuretics
Anesthetics	NSAIDs
Antibiotics	Opiates
Anticonvulsants	Organochloride pesticides
Antihistamine	Organophosphate pesticides
Antiparkinsonians	Pyrethroid pesticides
Antipsychotics	Sedative/hypnotics
Barbiturates	Steroids (corticosteroids)
Benzodiazepines	Stimulants
Beta-blockers	Other substances

Table 2 Toxic levels of substances

Substances	Blood concentration (mg/L)
Ethanol	> = 150 mg%
Methamphetamine	> = 0.15
Amphetamine	> = 0.2
Ketamine	> = 3.8
Morphine	> = 0.1
Methadone	> = 0.2
Cocaine	> = 0.5

myoglobin (1:200, Dako, Denmark) was used. The sections were examined with the light microscope under 100-fold magnification and divided semi-quantitatively into positive and negative. The positive myoglobin staining was used to conclude that rhabdomyolysis had occurred. The prevalence of the rhabdomyolysis was calculated.

These studied cases were then classified into two groups: suggestive of intoxication death and other causes of death, which included trauma and some sudden definite natural deaths, such as death from intracerebral hemorrhage or ruptured myocardial infarction. The suggestive of intoxication death referred to only toxic levels of drugs, such as ethanol that were detected or multiple drugs, was found. The definite cause of death group was used as the control group. The purpose of this separation was to find the relationship between rhabdomyolysis and the causes of death. The flow chart of this study is shown in Fig. 1.

Statistical analysis was performed using the SPSS and Stata software. The distribution of the data was tested using the Shapiro–Wilk test, and association was tested using a non-parametric test: chi-square.

Results

In this study, there were 50 cases consisting of 43 males and 7 females with a mean age of 36.2 years (the minimum was 16 years, and the maximum was 63 years).

The study group (suggestive of intoxication death) comprised 28 cases with a mean age of 38.25 years (the minimum was 16 years, and the maximum was 63 years). The demographic data and the frequencies of substances found are shown in Table 3. About 30% of this group were related with more than one substance.

The other cause of the death group (control group) consisted of 22 cases. The mean age was 33.64 years (the minimum was 17 years, and the maximum was 49 years). The demographic data, the causes of death and the frequencies of substances found are shown in Table 4. About 23% of this group were related with more than one substance.

In the study group, the positive myoglobin stain was found in 17 out of 28 cases (60.7%). There were 10 cases in which only one drug (including ethanol) was found. The number of cases found with multiple drugs was seven. The list of the illegal drugs is shown in Table 5.

In the control group, only 5 out of 22 cases (22.7%) were myoglobin positive. The myoglobin positive difference between the study and control groups was statistically significant (p = 0.007).

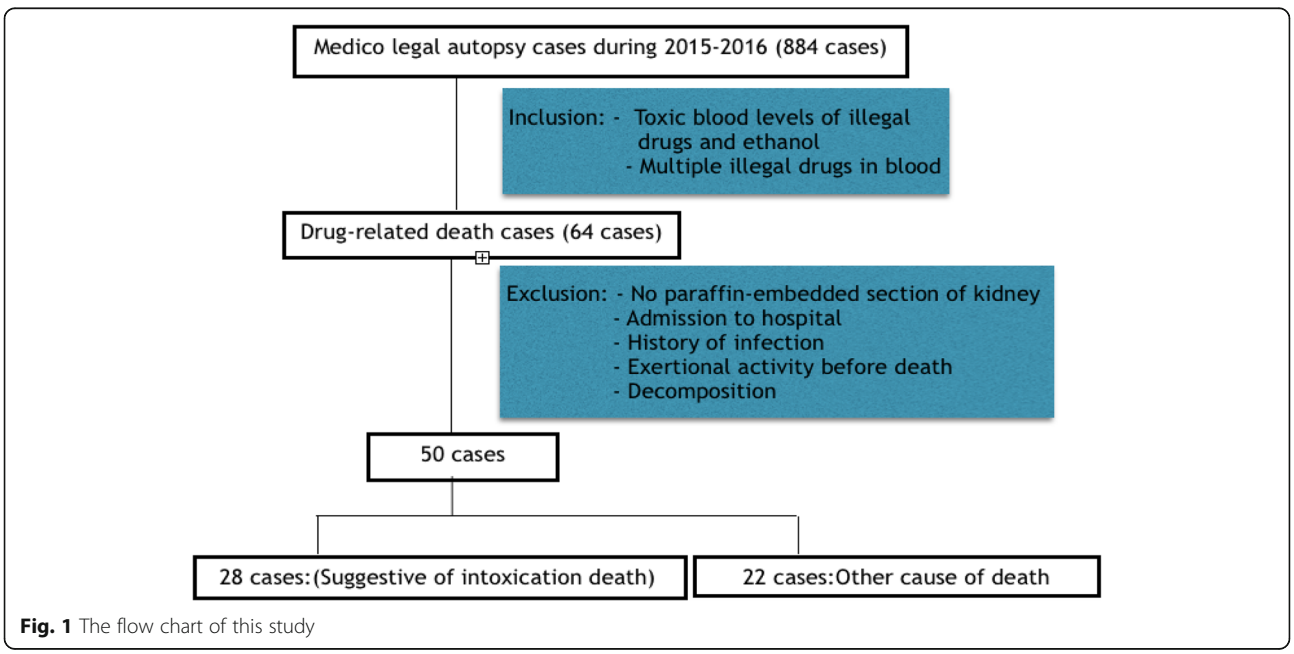

Fig. 1 The flow chart of this study

Table 3 The demographic data in the study group

Age (mean)	38.25 years
Sex (*n*, %)	Male = 25 (89.3)
	Female = 3 (10.7)
Found substances (*n*, %)	
Ethanol	11 (39.2)
Methamphetamine	5 (17.85)
Heroin	3 (10.7)
Methadone	1 (3.57)
Multiple drugs	8 (28.57)
Case 1	Methamphetamine, alprazolam, dextromethorphan
Case 2	Trihexyphenidyl, clozapine, haloperidol
Case 3	Ethanol, methamphetamine
Case 4	MDMA, MDA, codeine, morphine
Case 5	Methamphetamine, midazolam, morphine, codeine
Case 6	Cocaine, morphine, dextromethorphan
Case 7	Morphine, mitragynine
Case 8	Ketamine, morphine, 6-monoacetylmorphine
The organ mean weights (g, range)	
Lung : right	677.50 (270–1300)
Lung : left	557.67 (250–1150)
Heart	331.21 (240–460)
Brain	1337.50 (1050–1600)
Liver	1622.59 (950–2500)

Focusing only on the cases with a toxic level of ethanol (> = 150 mg%), there was a total of 23 out of 50 cases. Positive myoglobin in the kidney was found in 11 out of 23 cases (47.8%) separated into eight cases (72.7%) and three cases (27.2%) in the study and control groups, respectively. The difference between the two groups was still statistically significant (p = 0.022). These prevalence data are shown in Table 6. The data of each myoglobin positive case in the study group are shown in Table 7.

Discussion

To affirm illicit drugs and alcohol intoxication as the cause of death is very difficult for forensic pathologists. As a result, rhabdomyolysis eventuating in acute renal failure can help forensic pathologists to ascertain that the cause of death should be from illicit drugs and alcohol intoxication. As seen from many studies, various clinicians have indicated that drugs and alcohol are frequent causative agents in patients who develop rhabdomyolysis (Hohenegger, 2012; Ishigami et al., 2003; Welte et al., 2004; Richards, 2000; Melli et al., 2005).

The mechanism from using illicit drugs and alcohol has both a direct effect on the myocyte function or an indirect effect that predisposes the myocyte to develop injury (Richards, 2000; Melli et al., 2005; Curry et al., 1989). The direct effect is altering the calcium ion in the sarcoplasmic reticulum which causes the impairment of muscle adenosine triphosphate production (Richards, 2000; Melli et al., 2005; Curry et al., 1989; Pasnoor et al., 2014). This can cause a rupture in the cell membrane and a creatinine kinase leakage (Richards, 2000). Furthermore, the body's thermoregulatory mechanisms of heat production may fail, and the myocyte would not be able to maintain its function after using some drugs like stimulants (Ishigami et al., 2003; Liapis et al., 2016; Welte et al., 2004; Schulz et al., 2012; Winek et al., 2001; Richards, 2000; Melli et al., 2005; Curry et al., 1989; Pasnoor et al., 2014). There are several drugs that induce injury from the hypermetabolic mechanism including antipsychotics. Other stimulants like ketamine hydrochloride, as well as phencyclidine, can produce agitation and prolonged muscular activity that may contribute to muscle damage (Pasnoor et al., 2014).

This research showed rhabdomyolysis in the intoxication death group (study group) in which all were caused from drugs and ethanol-induced because all cases were selected by strict criteria. First, the illicit drugs and ethanol level displayed the toxic level or multiple illicit drugs in the blood. Then, the cases which had a history of infection or exertional activity before death were excluded.

Table 4 The demographic data in the control group

Age (mean)	33.64 years
Sex (*n*, %)	Male = 18 (81.8)
	Female = 4 (18.2)
Cause of death (*n*, %)	
Hanging	4 (18.2)
Drowning	2 (9.1)
Brainstem laceration	3 (13.6)
Aortic laceration	1 (4.5)
Liver laceration	2 (9.1)
Heart and lung laceration	1 (4.5)
Cervical spine injuries	1 (4.5)
Intracranial hemorrhage	1 (4.5)
Pulmonary embolism	1 (4.5)
Electrocution	1 (4.5)
Head injuries	2 (9.1)
Multiple organ injuries	3 (13.6)
Found substances (*n*, %)	
Ethanol	11 (50)
Methamphetamine	6 (27.3)
Multiple drugs	5 (22.7)
Case 1	Alprazolam,tramadol
Case 2	Methamphetamine, methadone
Case 3	Methamphetamine, midazolam, Morphine
Case 4	Ethanol, methamphetamine
Case 5	Ketamine, methamphetamine
The organ mean weights (g, range)	
Lung : right	503.64 (200–980)
Lung : left	444.55 (180–1150)
Heart	300.45 (200–420)
Brain	1272.73 (1150–1600)
Liver	1430.91 (970–2300)

Table 5 Percentages of common substances in study group

Substances	Number (%)
Ethanol	9 (39)
Opioids	5 (23)
Methamphetamine	4 (18)
Antipsychotics	1 (4)
Mitragynine	1 (4)
MDA,MDMA	1 (4)
Ketamine	1 (4)
Benzodiazepine	1 (4)

The trauma cases, which could induce a major cause of rhabdomyolysis (Zutt et al., 2014), were placed in the control group.

In the positive cases of the study group, the most common substance detected in the blood was ethanol like the previous study about drug and toxin-induced rhabdomyolysis (Curry et al., 1989).

Ethanol can cause rhabdomyolysis from a direct and secondary effect. The main mechanism in short-term alcoholic intoxication can alter the mental status, result in loss of consciousness, and sedation that can lead to prolonged immobilization and muscle compression. On the other hand, long-term alcohol consumption can present a history of poor nutrition, hypokalaemia, and hypophosphatemia, which can predispose the patient to rhabdomyolysis (Qiu et al., 2004; Papadatos et al., 2015).

The second most substance is opioids in which consumption can cause a prolonged phase of unconsciousness until developing pressure-induced necrosis of the muscle. If the position is maintained for a long time, the necrosis that develops will be high (Welte et al., 2004).

The next substance detected is methamphetamine. It stimulates sympathetic mechanisms to increase catecholamines, which induce muscular hyperactivity and severe hyperthermia and prolonged seizures. All of this can cause rhabdomyolysis (Ishigami et al., 2003; Welte et al., 2004; Pasnoor et al., 2014).

Compared with the control group, about 60% of the study group had rhabdomyolysis, which was significantly higher than the control group at 20%, although both groups were detected with toxic levels. This emphasized that detection of rhabdomyolysis in the cases that had no definite cause of death to be useful in concluding that death was a result from drug intoxication-induced rhabdomyolysis.

Various studies about rhabdomyolysis from drug-related deaths have been found in the forensic aspect. For example, Welte and Bohnert's study about the prevalence of rhabdomyolysis in 103 drug death cases in Germany in 2004 found rhabdomyolysis in 51 cases (50%) that was a higher number than the control groups (10%) (Welte et al., 2004). The diagnostic test for rhabdomyolysis applied the same method. Thus, this was a very useful diagnostic test in the autopsy case whereby there may be no other specimen like urine or blood.

In addition, Kock and Simonsen detected 20% of renal myoglobin from 62 drug addicts (Kock et al., 1994). A number of cases were detected with a lower level that may be due to the fact that the study cases were chronic drug addicts. As such, the cause of death may not be from the direct effect of the drugs. Unlike this research, selected cases that have toxic levels of drugs can produce rhabdomyolysis.

Table 6 Prevalence and comparison of rhabdomyolysis between the two groups

Group	Rhabdomyolysis		*p* value
	Positive, *n* (%)	Negative, *n* (%)	
All 50 cases			
Study group	17 (60.7)	11 (39.3)	0.007
Definite cause of death group (control)	5 (22.7)	17 (77.3)	
Ethanol level > = 150 mg%			
Study group	8 (72.7)	3 (27.3)	0.022
Definite cause of death group (control)	3 (25)	9 (75)	

In the cases that only ethanol was found, rhabdomyolysis in the study group was significantly higher than the control group. Four of eight positive myoglobin cases had an ethanol level greater than 150 mg% but not more than 200 mg%, which was the cause of obvious intoxication with nausea or a staggering gait, but no symptoms of stupor or coma. The remaining cases were found with an ethanol level greater than 200, but they did not have more than 350 mg% in which there was no respiratory center paralysis (Saukko & Knight, 2016). This emphasizes that the ethanol levels of 150–350 mg% could be the cause of death. In addition, one previous research found rhabdomyolysis in cases with 222 mg% of ethanol as well as diphenhydramine (Haas et al., 2003), but in the current study, only ethanol was found. However, ethanol metabolism depends on many factors and the multiple pathways of ethanol metabolism; therefore, the pathologist needs to evaluate each case.

The researchers of the present study also found multiple drug use but no quantitation in seven out of 17 cases. There were many types of substances found, which could cause death. Thus, the detection of rhabdomyolysis helped to confirm the cause of death, although there was no quantitation.

From Table 7, the current researchers also found that six out of the 12 cases had a history of drug addiction or heavy alcohol drinking. This means that rhabdomyolysis was not necessarily specific in people who used drugs or alcohol regularly. This supported the prevalence of rhabdomyolysis in this study more than Kock and Simonsen's study (Kock et al., 1994) about drug addicts.

Table 7 The data of each myoglobin positive case in the study group

No.	Gender	Age (years)	Substances and concentrations	History of drug/alcohol abuse	Circumstance of death
1	M	34	Ethanol 163 mg%	Social drinking	Sudden death (SUD)
2	M	33	Methamphetamine 0.051 mg/L	Drug addiction Heavy alcohol drinking	SUD
3	M	49	Methamphetamine 0.014 mg/L	Drug addict	SUD
4	M	51	Ethanol 323 mg%	Social drinking	Drinking alcohol before death
5	M	18	Morphine 0.09 mg/l Mitragynine 0.01 mg/l	Unknown	Abdominal pain and death on arrival
6	M	46	Ethanol 167 mg%	Unknown	SUD
7	M	54	Ethanol 198 mg%	Heavy alcohol drinking	SUD
8	M	48	Ethanol 224 mg%	Unknown	Drinking alcohol before going to bed
9	M	61	Ethanol 254.8 mg%	No	SUD
10	F	17	MDMA, MDA, morphine, codeine	Drug addict	Sudden death during drug use
11	M	49	Trihexyphenidyl, clozapine, haloperidol	Major depressive disorder	May be suicide
12	M	40	Ethanol 400 mg% methamphetamine	No	Drinking alcohol before death
13	M	26	Ketamine, morphine, 6-monoacetylmorphine	Drug addict	SUD
14	M	18	Cocaine, morphine, dextromethorphan	Unknown	No history
15	M	39	Ethanol 185 mg%	No	SUD
16	M	40	Methamphetamine, midazolam, morphine, codeine	Drug addict	SUD
17	M	63	Ethanol 324 mg%	Unknown	Drinking alcohol before death

The researchers also established that there was a history of drinking alcohol before death in only four of eight cases and only two out of eight cases with a history of drug use before death. This showed that the history and circumstance of death that indicated death from drug intoxication were often very rare. Therefore, the detection of rhabdomyolysis helped to find the cause of death in the absence of this section.

Conclusions

Deaths from drugs and ethanol intoxications are hard to confirm because of many factors such as drug tolerance. However, rhabdomyolysis is a common complication which may help the pathologists to certify the causes of deaths. Myoglobin detection in kidney by immunohistochemistry was used in this study to diagnose rhabdomyolysis in these drug-related death cases. From the study, most of the study group had rhabdomyolysis, which was significantly higher than the control group. Moreover, in the cases that only ethanol was found, rhabdomyolysis in the study group was also significantly higher than the control group. Therefore, rhabdomyolysis can be the one of important factors in the mechanism of death in drug-related death cases. Myoglobin detection in kidney by immunohistochemistry should be done to help for confirming the cause of deaths in these intoxication cases. However, the pathologist should conclude the cause of death carefully because the mechanism of death can be affected by several factors.

Abbreviations

CK: Creatinine kinase; SUD: Sudden death

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Authors' contributions

NK is initiating the study, collecting the data, analyzing the data, and writing the manuscript. SS is initiating the study, registering to the ethical approval committee, analyzing the data, writing the manuscript, and submitting the manuscript. KP is collecting the data and analyzing the data. WJ is collecting the data. All authors read and approved the final manuscript.

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Availability of data and materials

Please contact the authors for data requests.

Ethics approval and consent to participate

The analyses in this report have been approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (ID 04-59-50). The authors had informed consent from the legally authorized representative for collection of postmortem blood, and no identifiable personal data were presented in this manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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