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# Medical Autopsy for Sudden Unexplained Death in Saudi Arabia: A Call to Action

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## Abstract

Sudden unexplained death (SUD) is a sudden, unexpected, and unexplained death in an individual older than 1 year. It is one of the most devastating and tragic events to families and the community at large, particularly when it happens at a young age. Finding the cause of SUD is extremely important in order to prevent its recurrence in the family, and to help understand the epidemiology of SUD in the community. It has been well-established that the most effective way of finding the cause of SUD is by performing a medical autopsy. In many countries, medical autopsy is mandated in SUD cases. In others, however, medical autopsy is rarely performed for the purpose of identifying the cause of SUD, which is the case in Saudi Arabia. In this review, we discussed the importance of finding the cause of death in SUD cases, the role of different types of medical autopsies, and the state of medical autopsy in Saudi Arabia. Moreover, we proposed a clinical pathway to incorporate medical autopsy in the care of SUD cases, and to connect family members to the health care system in order to perform cascade screening.

**Keywords:** Sudden unexplained death, Sudden cardiac death, Autopsy, Saudi Arabia, Review article

## 1. Introduction

Sudden unexplained death (SUD) is a sudden, unexpected, and non-traumatic death in an individual older than 1 year [1]. It is one of the most devastating and tragic events to families and the community at large, particularly when it happens at a young age. Investigating SUD should be a public priority due to the important implications for families (identification of inherited conditions) and the community (many years of potential life lost). Beyond the value of “closure” to the grieving family, finding the cause of SUD guides family screening and informs preventative measures to prevent further tragic events. Post-mortem autopsy is the critical component of investigating SUD [1]. Indeed,

multiple studies have shown that autopsy identifies the cause of death in more than half of SUD victims [2–5]. Moreover, when the autopsy is negative, it narrows down the cause of death to a small number of primary arrhythmic disorders (i.e., sudden arrhythmic death syndrome, SADS), which could be identified by genetic testing and/or family screening. In Saudi Arabia, however, autopsies are seldom performed for the purpose of identifying the cause of SUDs [6]. This is despite the clear Fatwa from religious authority indicating that it’s permitted in Islam. We intend in this review to discuss the importance of medical autopsy in SUD, describe the practice and challenges of performing autopsies in Saudi Arabia, and suggest a pathway to implement medical autopsy in the care of SUD victims.

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## 2. Epidemiology of SUD

Sudden cardiac death (SCD) in the elderly most commonly occurs in the context of structural heart disease. In contrast, however, SCD is often the sentinel event in young adults and children with inherited arrhythmia conditions (i.e., SUD). The incidence of SCD in young adults and children is estimated to be 1.3–8.5 per 100,000 patients-years [4,7,8]. Limited data are available concerning the epidemiology of SCD in Saudi Arabia. Nofal et al. investigated a total of 1273 deaths at a university hospital in Dammam and reported a prevalence of SCD of 17.5%. Only 15% of them had a previous diagnosis of a cardiovascular disease. Importantly, 15.2% of them were young adults and children aged 1–40 years old [9]. While this is likely a biased estimate given that it was collected in a hospital setting, it provides some evidence suggesting that SCD at young age is not a trivial problem in Saudi Arabia, which should not be surprising given that 69% of the population is younger than 40 years of age [10].

Causes of SCD are strongly influenced by age, where coronary artery disease (CAD) is the most common cause in individuals older than 50 years old and rare for those younger than 35 years old [1]. Inherited arrhythmia conditions such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and long QT syndrome (LQTS) are the predominant cause of SCD for younger individuals up to the age of 50-year-old [2–4,7,11,12]. No studies have examined the incidence or causes of SUD among Saudis.

## 3. The yield of invasive autopsy in identifying the cause of death in SUD

An autopsy or a post-mortem examination (PME) is a process used for the detection of causes of death and other diseases. It is also a method to obtain specimens for microbiological, electron microscopy, molecular and genetic investigations. Death certificates are a major source of statistical data for identifying public health problems, monitoring progress in public health, allocating research funds, and conducting scientific research. Every effort must be made to ensure that the most specific, accurate and complete information regarding cause of death is registered on death certificates.

Proper reporting of death certificates, and performing a PME when needed, is very effective in finding the cause of death in the vast majority of SUDs. While the yield of autopsy may vary from study to study, most studies are able to identify the

### Abbreviations

SUD	Sudden unexplained death
SADS	sudden arrhythmic death syndrome
SCD	Sudden cardiac death
CAD	Coronary artery disease
HCM	Hypertrophic cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
LQTS	Long QT syndrome
PME	Post-mortem examination
VUS	Variants of uncertain significance
MRI	Magnetic resonance imaging
CT	Computer tomography
ARPKD	Autosomal recessive polycystic kidney disease
CPVT	Catecholaminergic polymorphic ventricular tachycardia
ICD	Implantable cardioverter-defibrillator

cause of death or at least narrow it down to a limited number of primary SADS causes [2–5]. For example, Puranik et al. performed a retrospective investigation of the cause of death of 427 sudden, non-traumatic death cases aged 5–35 in Eastern Sydney, Australia, and PME revealed the cause of death in 67% of the cases [2]. Multiple retrospective studies reported similar results, including studies performed in Ontario, Canada and Ireland, which reported a similar yield of 72% and 73% among SCD cases, respectively [3,4].

A prospective cohort study by Olallo Sanchez et al. revealed more details about the importance of autopsy and the addition of further testing such as molecular autopsy in identifying the cause of death in SUD cases [5]. The study reported that a diagnosis was reached through a conventional autopsy in 81.1% of cases, with the majority being caused by cardiac issues (56.87%) [5]. Furthermore, the study reported that adding molecular autopsy revealed the cause of death in 40% of previously unexplained cases [5].

## 4. Non-invasive autopsy: molecular autopsy

Molecular autopsy, also known as post-mortem molecular testing, refers to the use of genetic analysis to probe SUD with negative-traditional autopsy, usually caused by an underlying inherited arrhythmogenic cardiac disease [13]. The inheritance of such diseases is mostly autosomal dominant, which indicates a higher risk of SCD in direct family members of the deceased [14]. Therefore, molecular autopsy is crucial for identifying the underlying pathogenic or likely pathogenic variants to help detect risks in other family members and to help prevent more sudden deaths in the family [13–15]. For an efficient diagnosis, a multidisciplinary team

including cardiologists, geneticists, forensic pathologists and psychologists, should be involved, as the process of investigating a sudden death begins with extracting DNA from blood or tissue collected at autopsy, followed by next generation sequencing and inclusive filtering of variants based on cardiomyopathy and channelopathy genes, then prioritization of variants to assess pathogenicity through bioinformatics pipelines [14–16].

Cann et al. analyzed 96 sudden cardiac death cases over a 13 years period and was able to make a molecular diagnosis in 15% of SADS and 18% of cardiomyopathy deaths by defining pathogenicity of sequence variants integrating family phenotype information and population genomic data [16]. Similarly, Campuzano et al. studied 44 post-mortem samples of infants who died suddenly with no definite cause of death after a complete autopsy. They were able to identify 121 rare genetic variants, 33.05% of them were novel and 39.66% were located in genes encoding ion channels or associated proteins [17]. Both of which concluded that molecular autopsy should be included in the forensic protocol when no conclusive cause of death is known [16,17].

Molecular autopsy is also used by proxy, which refers to the genetic testing (Whole Exome Sequencing) of parents and relatives of the deceased individual to presume the cause of death. Alghamdi et al. found it to be a helpful approach to consanguineous couples who lost one or more children and/or pregnancies with no DNA available from the deceased ones for testing. This study was done on 83 consanguineous Saudi couples and was able to molecularly inform genetic counseling in 43 out of 83 Saudi couples (52%) [18]. Similarly, molecular autopsy by proxy was done in 44 families with at least one death or lethal fetal malformation, where pathogenic or likely pathogenic variants were identified in 50% of the families and variants of uncertain significance (VUS) were identified in 34% of the families. Shamseldin et al. concluded that molecular autopsy by proxy is indeed a practical and high-yield alternative to traditional autopsy [19].

Challenges and concerns regarding molecular autopsy differ from one country to the other. For instance, in the United States of America, there is an increasing shortage of qualified medical examiners and medical insurance does not cover the cost of post-mortem molecular testing [15]. In Switzerland and other European countries, legal guidelines for genetic testing do not address the use of molecular tools for post-mortem genetic analyses in forensic practice [20]. According to van Driel et al., ethical, legal and financial problems emerge with attempts to increase genetic screening in the Netherlands, even after the

finding that 50% of families with SCD were diagnosed with a cardiogenetic disorder [21]. In Saudi Arabia, religion raises a major concern regarding autopsies, even though dissection is allowed if it is legally required [22]. Molecular autopsy offers a way to detect the cause of death without disrupting the Islamic principles. Although it is an important tool, the benefits will be limited without a traditional autopsy in SUDs and SCDS. Therefore, there is a need to reassess the policy regarding the performance of autopsies in our country [22].

## 5. Non-invasive autopsy: Virtual Autopsy (virtopsy)

Virtual Autopsy (virtopsy) is a relatively new method of performing an autopsy without the need for invasive procedures. Instead, it uses radiological techniques such as magnetic resonance imaging (MRI) or multi-slice spiral computer tomography (CT) in order to find the cause of death. While virtopsy has not replaced conventional invasive autopsy worldwide, it is a very useful alternative for performing an autopsy in countries with cultural and religious barriers to conventional autopsy, such as Saudi Arabia.

Since the use of virtopsy is not widespread, the number of studies comparing the yield of virtopsy to conventional autopsy is still limited. However, the majority of the studies suggest that it is relatively effective in finding the cause of death in a shorter time and with less distress to the family of the deceased [23–25]. For example, a prospective study of 29 autopsy cases reported that a virtopsy was able to reach the same conclusion as a conventional autopsy in two out of three cases [23]. Another study of 40 cases reported similar results with virtopsy independently finding the cause of death in 55% of the cases [24]. Most recently, the first virtopsy in Saudi Arabia was performed at King Khaled University Hospital and identified a radiologic findings consistent with an autosomal recessive polycystic kidney disease (ARPKD), which was confirmed by conventional autopsy [25].

The yield of a virtopsy can be improved significantly by the addition of CT-guided biopsies to the radiological testing, and this process is known as a minimally invasive autopsy. A prospective cohort study showed that while the yield of a standalone CT or MRI was limited, the use of a minimally invasive autopsy provided the answer to 84.5% of the cases [26]. Therefore, the use of minimally invasive autopsy could be a very effective and publicly acceptable way of performing an autopsy in Saudi Arabia.

### 6. The clinical value of autopsy in preventing SCD in family members

Performing an autopsy in individuals with SUD is strongly recommended by the recent guidelines [1]. This is because it guides the next step in the management of first-degree relatives. When the autopsy identifies the cause of SUD, clinical investigation will focus on screening the family for that specific cause, which is helpful because some of these conditions require expensive investigation (e.g., cardiac magnetic resonance for ARVC) or have a variable age presentation (e.g., HCM and ARVC) and as such need repeat testing. Even when the autopsy is negative (i.e., SADS), autopsy remains helpful as it narrows down the causes of death to a small number of primary arrhythmic conditions such as LQTS, Brugada syndrome, and Catecholaminergic

polymorphic ventricular tachycardia (CPVT). As such, the strategy by which we approach first degree relatives of a SUD victim is highly dependant on the results of the autopsy.

Because most of the causes of SUD at young age are related to inherited arrhythmia conditions, the primary goal of family screening is to identify these conditions to potentially prevent SCD in affected family members. This is particularly relevant given the available effective therapies for most of the conditions such as beta-blockers for LQTS and CPVT, and implantable cardioverter-defibrillator (ICD) for HCM. Also, important lifestyle modifications can modify the prognosis of some of these conditions and potentially prevent SCD, such as aggressive fever treatment in Brugada syndrome and avoidance of competitive sports in ARVC and HCM. Even when the cause of SUD is not a clearly

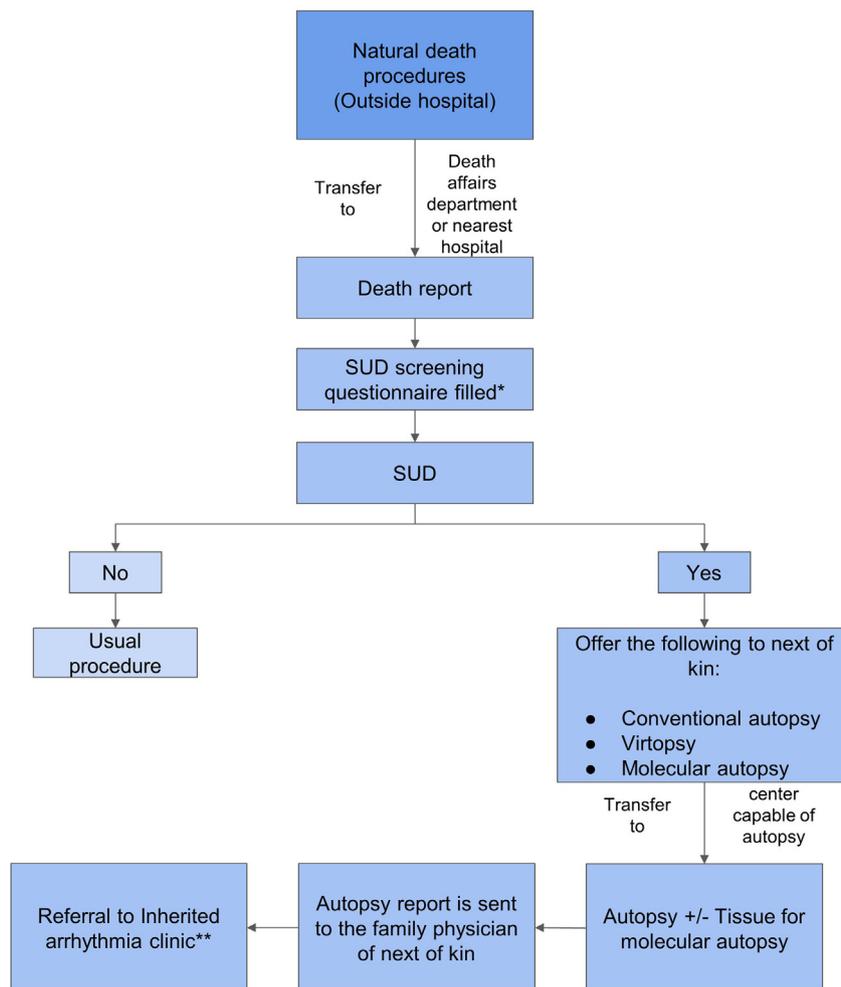


Fig. 1. Proposed pathway for medical autopsy: SUD: sudden unexplained death. \* SUD criteria: 1- Death occurring within an hour of onset of symptoms, or in patients found dead within 24h of being asymptomatic, 2- Unexplained by previous SCD-predisposing condition, toxin, homicide, or suicide. \*\* Inherited arrhythmia clinics are multidisciplinary clinics with a team including an electrophysiologist, medical geneticist, genetic counsellor, and a pathologist.

inherited condition (i.e., not a monogenic condition) such as early-onset CAD, there is likely a value of early diagnosis and aggressive treatment of risk factors in preventing SCD, given that these families are at higher risk of SCD due to CAD [27].

## 7. The state of medical autopsy in Saudi Arabia

Autopsies in most Muslim nations including Saudi Arabia, are performed by the department of forensic medicine under the direction of Ministry of Interior. Because of the perceived disfigurements, the medical environment is generally opposed to autopsy. A recent survey of 234 Saudi physicians and interns found that while most physicians (86.32%) think that an autopsy is important to perform, almost all of them (98.29%) have never taken part in an autopsy and only 4% were offered a chance to attend an autopsy session [28]. Moreover, the study reported that the main barriers to performing an autopsy were respect for the religious beliefs of the families of the deceased and respect for family mourning [28]. In the last several years after establishing a Saudi speciality training program, forensic medical education in Saudi Arabia expanded. However, both the system and training program focus on homicide and suspicious for homicide cases. There is no system for medical autopsies and no training program that trains pathologists to do medical autopsy [6,25]. As a result, there is no system in Saudi Arabia for medical autopsies of natural deaths, although preliminary acceptance of this service is pending at the college of Medicine, King Saud University, following the Centers for Disease Control and College of American Pathologists guidelines [29].

## 8. Proposed pathway for autopsy in SUD cases in Saudi Arabia

Performing a medical autopsy is the cornerstone of finding the cause of SUD. It can facilitate family screening with the ultimate goal of preventing SCD in these families. There is an urgent need to establish a clear pathway to implement medical autopsy for SUD cases in Saudi Arabia. Fig. 1 shows our proposed pathway to include medical autopsy for SUD and link family members to the health care system in order to perform cascade screening. The pathway starts when a natural death occurs, and a death report is written. We suggest adding a questionnaire that screens the case for SUD by checking for the following SUD criteria: 1- Death occurring within an hour of onset of symptoms, or in patients

found dead within 24h of being asymptomatic, 2- Death is not due to homicide, suicide or explained by an established SCD-predisposing condition or a toxicology screen. If the case fulfils the criteria, the next of kin are offered the following options: conventional autopsy or virtopsy/minimally invasive autopsy (+/-molecular autopsy). After performing the chosen autopsy, the autopsy report is sent to the family physician of the next of kin and the family are consulted about the cause of death. Then, all first degree relatives are referred to a specialized and multidisciplinary clinic (inherited arrhythmia clinic) which includes a cardiologist, medical geneticist, genetic counsellor and a pathologist, where a complete evaluation will be performed. This will obviously require a network of clinics and a collaboration between death affairs departments and these clinics.

## 9. Conclusion

SUD is a devastating event and one that needs thorough investigation in order to prevent its recurrence in the family. There is no system in place in Saudi Arabia to perform medical autopsy and family screening in SUD cases. Our review calls for an urgent change to implement routine medical autopsy and family screening with the ultimate goal of preventing SCD in affected families. In addition, we proposed a clinical pathway to enable these services.

## Author contribution

Conception and design of Study: WA. Literature review: WA, AA, MA, AH, TK, KA. Drafting of manuscript: WA, AA, MA, AH, TK, KA. Revising and editing the manuscript critically for important intellectual contents: WA, AA, MA, AH, TK, KA. Supervision of the research: WA. Research coordination and management: WA.

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## Conflict of interest

None disclosed.

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