Post COVID-19 vaccine deaths - Singapore's early experience

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ABSTRACT

Singapore has been using mRNA vaccines developed by Pfizer-BioNTech and Moderna as part of the nation's COVID vaccination program since 30 December 2020. From 1 February 2021–30 June 2021, a total of 34 deaths that occurred within 72 h of the deceased receiving their COVID-19 vaccination were referred to the Forensic Medicine Division of the Health Sciences Authority of Singapore. Autopsies, histological sampling and ancillary investigations consisting of total tryptase level, Immunoglobulin E (IgE), and C-reactive Protein (CRP), were performed on 29 of these cases. Our study has shown no definite causative relationship between the mRNA vaccination and deaths of individuals who died within 72 h after receiving the vaccination, in particular with regards to anaphylactic reactions, myocarditis and pericarditis, and thrombotic complications. Further studies may consider increasing the incident time frame from 72 h to seven days post-vaccination or longer to include any potential delayed presentation of adverse effects.

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1. Introduction

The SARS-CoV-2 virus is a positive-sense single-stranded RNA coronavirus that is responsible for the ongoing COVID-19 pandemic [1,2]. With over 183 million confirmed cases and almost 4 million deaths worldwide as of 2 July 2021 [3], the virus has been shown to be able to spread rapidly and overwhelm healthcare facilities.

Four main pillars of infection control are being used internationally to curb the spread and mortality of the disease: border control, community lockdowns, contact tracing and quarantine, and pre-emptive vaccination. While border controls and community lockdowns have been shown to reduce the transmission of the SARS-CoV-2 virus, they have also greatly affected the community and economy, and cannot continue endlessly. Contact tracing and quarantine are ongoing, but have limited power and require sufficient manpower, quarantine facilities, and compliance of the infected patients. Vaccination hopes to immunize the population to allow the safe reopening of local and international communities while reducing risks of infection and mortality from the virus.

Since the publishing of the SARS-CoV-2 genome, scientists have worked rapidly to develop effective vaccines. Different vaccination strategies have been used, including but not limited to inactivated [4,5] and protein subunit vaccines [6], viral vector vaccines [7–9], and mRNA vaccines [10–12]. While the technology to develop the latter is not new, having been proposed and in the midst of research for viral targets such as HIV-1, Influenza, and Zika viruses [13], the BNT162b2 COVID-19 vaccine was the first to be authorized for widespread use [14]. Research has shown that the BNT162b2 vaccine has been 95% effective in preventing COVID-19 [11], yet hesitancy to take the vaccine remains, possibly due to the lack of trust in vaccines that were developed very rapidly and fears of possible side effects.

In Singapore, border controls, community lockdowns (termed locally as "circuit breakers"), contact tracing and quarantines, and vaccination have helped to reduce the national incidence of COVID-19 infections, with 62,599 confirmed cases and 36 deaths as of 2 July 2021 [3].

The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines comprise Singapore's COVID-19 Vaccination Program [15,16]. The Pfizer-BioNTech vaccine was first given to healthcare workers starting 30 December 2020 [17], and subsequently offered to senior citizens and then to the general public aged 16 and above. Interim authorization of the Pfizer-BioNTech vaccine for the vaccination of children between 12 and 15 years of age was granted on 18 May 2021 [18]. The Moderna vaccine was the second mRNA vaccine made available to individuals aged 18 years and above, beginning on 17 March 2021 [19]. As of 2 July 2021, approximately 3.42 million (58.57%) of the population in Singapore have received at least the 1st dose of either the Pfizer-BioNTech or Moderna COVID-19 vaccination, and 2.13 million (36.33%) have been fully vaccinated with either of the COVID-19 vaccines [3].

With the large vaccination exercises locally and internationally, there would inevitably be some whose demise was temporally close

to their receiving of a COVID-19 vaccine, raising questions if the death was related to their recent vaccination. COVID-19 vaccine-related adverse events have also been reported in the literature, including anaphylaxis [20–26], myocarditis and pericarditis [27–34], and thrombosis with thrombocytopenia syndrome [35–37]. Establishing vaccine safety is of utmost importance to protect the intended audience, *primum non nocere*, and for allaying fears which might otherwise cause vaccine hesitancy.

The Forensic Medicine Division, Health Sciences Authority is the national center for the review of coronial cases, including deaths where the cause is unknown, or if they may have occurred as a result of recent medical treatment or care. The Forensic Medicine Division has been accredited by the National Association of Medical Examiners since 1 March 2016. All cases referred for coronial investigation undergo a post-mortem computed tomography (PMCT) as per established departmental protocol. Each coronial case is reviewed by the duty pathologist, including the deceased's medical history, circumstances of death, and the results of the PMCT scan. Information on medical history, vaccination status and dates of vaccination are obtained through the National Electronic Health Records. The pathologist then discusses with the coroner if an autopsy is required. If the death occurred within 72 h after the deceased had received the COVID-19 vaccination, or the death is suspected to be related to the vaccination, a post-mortem is currently recommended unless there is evidence of catastrophic causes of death, such as a ruptured aortic aneurysm, which would be highly unlikely to be related to the recent vaccination. In cases where the death was deemed very unlikely to be due to the reported vaccine-related adverse effects following a detailed review of the deceased's past medical history, the circumstance of death, and review of the PMCT findings, a cause of death may be given without an autopsy at the discretion of the coroner. A thorough external examination of each coronial case is conducted if an autopsy is not performed.

In this study, we perform a retrospective analysis of coronial cases where the demise occurred soon after COVID-19 vaccination to investigate if there is any evidence of causation between COVID-19 vaccination and deaths so far.

2. Methods

All coronial cases between 1 February 2021 and 30 June 2021 who had died within 72 h of receiving a dose of either the Pfizer-BioNTech or Moderna vaccine, or sustained neurological or cardiovascular compromise requiring medical resuscitation within 72 h of receiving the vaccine and subsequently demised after a period of hospitalization, were included in this study. There were no reported cases of individuals who had died or collapsed within 72 h of receiving their vaccination before 1 February 2021. Autopsies were performed according to established departmental procedures, and close attention was paid to look out for findings of anaphylaxis and local allergic reactions. Dissection of the vaccination site was performed if the vaccination site could be determined. Histological sampling was performed according to a departmental post-vaccination protocol (Table 1), including specimens of all major organs and the injection site, if identified. Other ancillary investigations performed included levels of total tryptase, Immunoglobulin E (IgE), and C-reactive Protein (CRP). Post-mortem blood samples for these ancillary investigations were obtained by "milking" the vessels of the lower limbs and collecting the blood from the cut-ends of the femoral vessels during evisceration of the body. Histological slides were screened for the presence of eosinophilic infiltrations, myocarditis, and thrombosis.

Data comprising patient demographics, type of vaccine administered, if it was the first or second dose of the vaccine, the number of days post-vaccine before the demise or collapse, the cause of death, and the results of the ancillary investigations were extracted and recorded. Each case was anonymized and recorded with Microsoft Excel.

Table 1
Departmental Post-Vaccination Histology Sampling Protocol.

Sample Site	Minimum Number of Sections
Cerebrum	3
Cerebellum	1
Pituitary	1
Enlarged Axillary Lymph Nodes	1
Lungs	5
Trachea	1
Main Bronchi	1
Aorta	1
Heart	5 (1x right ventricle, 4x left ventricle)
Coronary Arteries	2 (from different arteries)
Liver	1
Pancreas	1
Spleen	2
Adrenal Glands	2
Kidneys	2
Terminal Ileum	2
Bone Marrow	2
Vaccination Site	1 (if identified)

3. Results

A total of 33 cases were identified and included in this study (Table 2). They comprised 26 males (78.8%) and 7 females (21.2%), with a median age of 69 years (23–96 years). 20 were Chinese (60.6%), 8 were Malays (24.2%) and 5 were Indians (15.2%).

The cause of death was issued in 5 cases (15.2%) without an autopsy, as there was evidence of catastrophic causes of death and/or the cause of the death was deemed highly unlikely to be related to the vaccination after reviewing the circumstances of death, the antemortem clinical notes, and the PMCT. Autopsies were performed on the remaining 28 cases (84.8%). The cause of death was deemed to be natural in 31 cases (93.9%) and unnatural in 2 cases (6.1%).

28 and 5 cases received the Pfizer-BioNTech and Moderna vaccines respectively (84.8% and 15.2% respectively). 13 cases (39.4%) received their first dose and 20 cases (60.6%) received their second dose. Death or collapse occurred on the day of, 1 day after, 2 days after, and 3 days after the vaccine (either the first or second dose) in 8 cases (24.2%), 14 cases (42.4%), 8 cases (24.2%) and 3 cases (9.1%) respectively.

Of the cases that had an autopsy performed, none demonstrated signs of anaphylaxis (facial swelling, angioedema and/or laryngeal edema). 1 case (3.6%, case no. 16) showed an acute coronary thrombus at autopsy, which was confirmed histologically with no evidence of vasculitis or eosinophilic infiltration. This deceased had known underlying ischemic heart disease, with previous percutaneous coronary intervention (PCI) performed to the left anterior descending artery (LAD) and the right coronary artery (RCA). The thrombus was located immediately distal to the RCA stent, and appeared acute both macroscopically and microscopically.

At autopsy, if the vaccine injection site was identified, layered dissection and examination of the skin, subcutis, major blood vessels and nerves, and lymph nodes were performed. Macroscopically, most cases showed mild subcutaneous fat and deltoid muscle hemorrhage, as expected following local trauma due to the injection needle. None showed major hemorrhage, necrosis, or abscess formation. Microscopic examination of the injection site showed no evidence of necrosis, vasculitis, neuritis or eosinophilic infiltration.

The majority (22 cases, 78.6%) had serum total tryptase levels less than 43, while 6 cases (21.4%) had levels greater than 43. Of these 6 cases, 2 cases (cases 7 and 28) were witnessed sudden collapses while case 29 was found unresponsive at home while having a shower. All 3 cases did not report symptoms of an allergic reaction or anaphylaxis prior to their collapse. All 3 cases were aggressively resuscitated and intubated in the emergency department. No rash, facial or periorbital swelling, or airway edema was noted during

Table 2
Detailed Information Regarding All Cases.

| | Demographics of Coronial Post-Vaccination Deaths | | | | | | | Results of Ancillary Investigations Performed | | | | |
Case No.	Age	Gender	Vaccine	Dose	Number of days post-vaccination	Autopsy	Cause of Death	Signs of Anaphylaxis[a]	Total Tryptase (ug/l)	IgE (IU/mL)	CRP (mg/L)	Histological Features[b]
1	86	Female	Pfizer-BioNTech	1	2	Yes	Spontaneous acute right intracerebral hemorrhage	No	5.3	N.A.[c]	197	No
2	67	Male	Pfizer-BioNTech	1	2	Yes	Sigmoid volvulus	No	4.4	N.A.[c]	28.8	No
3	74	Male	Pfizer-BioNTech	1	0	Yes	Coronary artery disease	No	18.7	28.8	1.9	No
4	86	Male	Pfizer-BioNTech	1	2	Yes	Bleeding duodenal ulcer	No	5.8	129	18.4	No
5	63	Male	Pfizer-BioNTech	2	1	Yes	Ischemic heart disease	No	20.2	2529	1	No
6	67	Male	Pfizer-BioNTech	2	3	Yes	Hypertensive and ischemic heart disease	No	18.9	23.9	3.9	No
7	76	Male	Pfizer-BioNTech	2	2	Yes	Ischemic heart disease	No	102	27.5	21.2	No
8	91	Male	Pfizer-BioNTech	2	1	Yes	Ruptured acute myocardial infarction	No	6.1	311	89.8	No
9	76	Female	Pfizer-BioNTech	2	1	Yes	Subarachnoid hemorrhage due to ruptured berry aneurysm	No	20.1	62.9	7	No
10	80	Male	Pfizer-BioNTech	1	0	Yes	Ischemic heart disease	No	8.1	4405	1.7	No
11	86	Male	Pfizer-BioNTech	2	1	Yes	Ischemic heart disease	No	6.2	1	4.8	No
12	94	Female	Pfizer-BioNTech	2	1	Yes	Hypertensive heart disease	No	14.9	113	1	No
13	69	Male	Pfizer-BioNTech	2	0	Yes	Ischemic heart disease	No	17.7	502	0.3	No
14[d]	72	Male	Pfizer-BioNTech	1	0	No	Pneumonia	-	-	-	-	-
15	63	Male	Pfizer-BioNTech	2	0	Yes	Ruptured ascending aortic dissection	No	9.2	245	0.6	No
16	53	Male	Pfizer-BioNTech	1	1	Yes	Acute right coronary thrombosis	No	7.4	Rejected	Rejected	Yes
17	69	Male	Pfizer-BioNTech	2	0	Yes	Severe interstitial lung disease with coronary artery disease	No	4.8	17.8	19	No
18[d]	72	Female	Pfizer-BioNTech	2	1	No	1a) Sepsis from pneumonia and UTI b) Acute myocardial infarction	-	-	-	-	-
19	23	Male	Pfizer-BioNTech	2	1	Yes	Severe obesity, with associated cardiomyopathy, hypoventilation syndrome and obstructive sleep apnea	No	> 200	594	16.8	No
20	80	Male	Pfizer-BioNTech	1	3	No	Coronary artery disease with chronic obstructive pulmonary disease	-	-	-	-	-
21[d]	65	Male	Moderna	2	1	Yes	Head injury	No	39.2	173	28.1	No
22[d]	56	Male	Moderna	2	1	Yes	Cerebral infarction with hemorrhage	No	> 200	35.3	Rejected	No
23	52	Male	Pfizer-BioNTech	1	1	Yes	Coronary artery disease	No	28.8	9.6	5.5	No
24	53	Male	Moderna	2	2	Yes	Right coronary artery anomalous origin with atherosclerotic ostial stenosis	No	9.1	279	17.3	No
25	51	Male	Moderna	2	3	Yes	Coronary artery disease	No	20.4	19.8	5.9	No
26	53	Female	Pfizer-BioNTech	2	1	Yes	Coronary atherosclerosis	No	8.4	42.5	10.1	No
27[d]	33	Male	Moderna	2	1	Yes	Consistent with multi organ failure following cardiac arrest due to right ventricular dysplasia	No	10.3	243	155	No

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Table 2 (*continued*)

Case No.	Age	Gender	Vaccine	Dose	Number of days post-vaccination	Autopsy	Cause of Death	Signs of Anaphylaxis[a]	Total Tryptase (ug/l)	IgE (IU/mL)	CRP (mg/L)	Histological Features[b]
28	39	Male	Pfizer-BioNTech	1	0	Yes	Ischemic heart disease	No	43.4	513	2.4	No
29	72	Female	Pfizer-BioNTech	1	2	Yes	Ischemic heart disease	No	44.5	6.3	0.5	No
20	60	Male	Pfizer-BioNTech	1	2	Yes	Ischemic heart disease	No	9.7	24	2.3	No
31	96	Female	Pfizer-BioNTech	2	2	No	Coronary artery disease	–	–	–	–	–
32	86	Male	Pfizer-BioNTech	1	0	No	Hypertensive heart disease	–	–	–	–	–
33	67	Male	Pfizer-BioNTech	2	1	Yes	Head injury	No	52	59.3	3.2	No

Table 2 lists the details of all 33 cases of this study, comprising 28 who had undergone an autopsy and 5 cases who were not subjected to an autopsy. The majority (84.8%) of the cases received the Pfizer-BioNTech vaccine as this was the first and initially only vaccine available in Singapore at the time. No signs of anaphylaxis or histological features suggesting anaphylaxis, myocarditis and thrombosis were present in all cases who underwent an autopsy. Serum total tryptase was greater than 43 in 6 cases.

a Refers to signs such as facial (including periorbital, lips etc.) or airway edema, skin changes (e.g. rash, urticaria)

b Refers to the presence of eosinophilic infiltration, the presence of myocarditis and/or thrombosis

c Not part of initial sampling protocol

d Cases who sustained neurological or cardiovascular compromise requiring medical resuscitation within 72 h of receiving the vaccine and subsequently demised after a period of hospitalization

resuscitation. The autopsy of these 3 cases showed multiple bilateral rib fractures consistent with cardiopulmonary resuscitation. The causes of death of these 3 cases were given as ischemic heart disease after the autopsy. Case 33 suffered a fall and sustained a traumatic head injury with a skull fracture, subdural and subarachnoid hemorrhages, and cerebral contusions. Lung and splenic tissue from cases 7, 28, 29, and 33 were submitted for further histological evaluation and stained with anti-mast cell tryptase antibody (AA1 clone; DAKO M7052 protocol). Very scattered mast cells staining positively for anti-mast cell tryptase antibody were seen in the lung tissue and only focally present in the splenic tissue of these cases (< 1–1 per x40 field). Case 19 was found unresponsive at home, 1 day after receiving his second dose of the Pfizer-BioNTech vaccine. He had no recorded allergic reactions to his first vaccine dose and had been well after receiving his second dose. He had an extensive medical history of obesity with a body-mass index of 68 kg/m^2, obesity hypoventilation syndrome, severe obstructive sleep apnea, asthma, hypertension, gastritis and was a chronic smoker. At autopsy, no facial swelling, airway swelling or rash was present. The heart showed features in keeping with obesity and hypertension-related changes and there was no eosinophilia present in the organs on histological evaluation. The cause of death was given as severe obesity, with associated cardiomyopathy, hypoventilation syndrome, and obstructive sleep apnea. Case 22 developed acute left-sided weakness 1 day after being vaccinated and was diagnosed with an acute right cerebral infarction complicated by severe malignant cerebral edema and intraventricular hemorrhage. He underwent decompressive neurosurgery but demised 8 days after his initial admission. The cause of death was given as cerebral infarction with hemorrhage. Lung and splenic tissue from cases 19 and 22 were submitted for histological evaluation and stained with anti-mast cell tryptase antibody (AA1 clone; DAKO M7052 protocol). There was an increased amount of mast cells staining positively for anti-mast cell tryptase antibody in the lung tissue. Splenic tissue from case 19 showed about 2.5 positively-staining mast cells per x40 field, while splenic tissue from case 22 showed < 1 positively-staining mast cells per x40 field.

Testing for IgE levels was rejected for 1 case (3.7%) and was not sent in 2 cases (7.4%) due to a change in sampling protocol. Of the remaining 25 cases, 13 cases (52.0%) had IgE levels less than < 100 IU/mL while 12 cases (48.0%) had IgE levels > 100 IU/mL. Elevated concentrations of CRP were found in cases 1 (197 mg/L) and 27 (155 mg/L). Both cases showed evidence of sepsis which would account for the elevated inflammatory marker concentration. At autopsy, case 1 showed pneumonia with consolidation changes in the lungs. Case 27 developed multi-organ failure and sepsis after suffering a cardiac arrest due to right ventricular dysplasia.

4. Discussion

The main classes of vaccines that are currently being used are the inactivated vaccines, viral vector vaccines, and mRNA vaccines. CoronaVac and BBIBP-CorV, inactivated vaccines developed by Chinese biopharmaceutical companies Sinovac and Sinopharm, respectively, have not reported any anaphylactic events in their Phase 3 trials [38]. Viral vector vaccines, in particular ChAdOx1, have seen an incidence of thromboembolic events – predominantly venous – in individuals who have received the vaccination [35,39], although data from Denmark suggests that the reported number does not seem to be increased relative to the expected number estimated from pre-vaccination incidence rates [40].

The adverse side effects attributed to the mRNA vaccines have been widely reported, including acute local allergic reactions, systemic anaphylaxis, myocarditis and pericarditis. Rare cases of thrombotic thrombocytopenic purpura (TTP), initially reported in individuals who received viral vector vaccines, have also been

reported in individuals inoculated with the Pfizer-BioNTech vaccine [41–43]. In Singapore, as of 30 June 2021, 6606 suspected cases of vaccine-related adverse effects were reported, of which 252 were assessed as serious. The most frequently reported serious adverse effects were anaphylaxis and other severe allergic reactions. Out of a total of 5470,425 doses of the mRNA vaccines administered, there were 42 cases of anaphylaxis and 12 cases of myocarditis and pericarditis reported. All reported cases of serious adverse effects were non-fatal. A greater frequency of heart attacks and strokes has not been observed in vaccinated persons locally. Due to the large numbers of people being vaccinated, it is expected that, by coincidence, some individuals may experience medical events such as heart attacks and strokes in the days or weeks after vaccination which may not be related to the vaccination [44].

The acute allergic responses caused by vaccines stem from the activation of mast cells mediated by the interaction between IgE antibodies against the vaccine. This type I hypersensitivity reaction occurs within minutes or up to four hours. The type IV or delayed hypersensitivity reactions initiate 48 h after vaccination and peak between 72 h and 96 h after vaccination [45]. Early safety monitoring data of both the Pfizer-BioNTech and Moderna vaccines showed that most cases of anaphylaxis to the vaccines had symptom onset within 30 min of vaccination, with the longest duration between vaccination and symptom onset being 150 min [20,21]. A rare case of biphasic anaphylactic reaction to the first dose of the Pfizer-BioNTech vaccine was also reported, where the individual developed symptoms three days post-vaccination after being initially treated for anaphylaxis within a few minutes of being vaccinated [46].

Our study is the Singapore study for the first six months of vaccine usage. The selection of the 72-hour post-vaccination time period for the study was primarily to investigate acute allergic responses, as it was the major concern when the government was advising the population to be vaccinated earlier in the year [47]. Delayed hypersensitivity reactions, myocarditis, pericarditis and thrombosis which may happen within this timeframe were also investigated. This study has shown no definite causative relationship between the mRNA vaccination and deaths of individuals who died or suffered neurological or cardiovascular collapse within 72 h after receiving the vaccination, in particular with regards to anaphylactic reactions, myocarditis and pericarditis, and thrombotic complications. There was no evidence of vaccine-induced thrombotic thrombocytopenia or dural venous sinus thrombosis in all cases. This is similar to the findings established by Elder et al. in their case series of deaths associated with the BNT162b2 in Hamburg, Germany [48].

Histological evaluation of all post-mortem cases has revealed no evidence of eosinophilia, myocarditis or vasculitis-induced thrombotic events. Rare cases of elevated serum tryptase and/or serum IgE without signs of anaphylaxis at autopsy were noted. While elevated levels of serum tryptase and IgE with the accompanying clinical manifestations would be diagnostic of anaphylaxis, elevated serum tryptase and IgE levels in isolation are difficult to interpret in the post-mortem setting [49]. Edston concluded that it is possible to diagnose anaphylaxis with a high degree of certainty by quantifying eosinophil granulocytes and mast cells in the spleen in combination with tryptase measurements in serum [50]. While major basic protein (MBP) immunohistochemical stain is not available in our laboratory, no eosinophilia was evident on histological evaluation of tissues from all our cases. Anti-mast cell tryptase immunostain performed on cases with raised serum tryptase do not show increased immunostaining characteristic of anaphylaxis. Raised serum tryptase concentrations have been observed in deaths due to coronary heart diseases, and also noted in other diseases such as end-stage renal failure, acute myelocytic leukemia and myelodysplastic syndromes. The post-mortem interval, hemolysis, and trauma may also affect the post-mortem tryptase concentration [49,51,52]. The

increase in tryptase concentration in cases that have sustained trauma may account for the elevated tryptase concentrations in cases 7, 28, 29 and 33, as the first 3 cases were documented to have received aggressive cardiopulmonary resuscitation and case 33 sustained a traumatic head injury. Mast cells are known to be the first responders to intracerebral hemorrhage and release potent mediators – including tryptase – when activated [53], as in case 22. Fenger et al. found that body-mass index and smoking were positively associated with serum tryptase levels [54]. Serum tryptase concentrations were also found to be significantly higher in asthmatic children and especially obese asthmatic children [55]. We postulate that the extensive medical history of obesity, asthma and smoking, of case 19 may have contributed to his elevated tryptase levels. Moreover, case 19 also suffered from severe obstructive sleep apnea, which is known to be associated with airway inflammation and remodeling, as well as increased airway mast cells and tryptase levels [56]. Obstructive sleep apnea is also seen in cases of mast cell activation syndromes [57], although this diagnosis was not definitively made in case 19. Thus, with many variables, no clear diagnostic features of anaphylaxis both clinically and at autopsy and with no increased immunostaining for mast-cell tryptase in the splenic tissue sample, the cause of death was attributed to severe obesity, with associated cardiomyopathy, hypoventilation syndrome and obstructive sleep apnea. Elevated post-mortem IgE concentrations are in themselves not conclusive as evidence of death due to IgE-mediated anaphylactic shock, but rather indicate that sensitization of a specific allergen took place before death [58].

At the time of this study, the majority of the population vaccinated were above the age of 50. There is now a growing number of younger individuals registering for their first dose of the vaccination. While the incidence of post-vaccination myocarditis and pericarditis in the local population has been low, countries with a larger number of vaccinated children and young adults have reported a significant incidence of myocarditis and pericarditis following mRNA COVID-19 vaccination. The onset of symptoms of post-vaccination myocarditis and pericarditis may be as delayed as seven days after vaccination [59]. As Singapore continues to extend the mRNA vaccinations to older children and young adults, there is a need to continue investigating deaths temporally close to the individual receiving their COVID-19 vaccination. Further studies may consider increasing the incident time frame from 72 h to seven days post-vaccination or longer to include any potential delayed presentation of adverse effects, such as delayed hypersensitivity reactions, myocarditis and pericarditis.

5. Conclusion

Our study has shown no definite causative relationship between the mRNA vaccination and deaths of individuals who died or collapsed within 72 h after receiving the mRNA COVID-19 vaccination with regards to anaphylactic reactions, myocarditis and pericarditis, and thrombotic complications. Further studies may consider increasing the incident time frame from 72 h to seven days post-vaccination or longer to include any potential delayed presentation of adverse effects.

CRediT authorship contribution statement

Audrey YEO: Conceptualization, Writing – original draft, Writing – review & editing. **Benjamin KUEK:** Methodology, Writing – original draft, Writing – review & editing. **Mandy LAU:** Investigation, Writing – original draft, Writing – review & editing. **Shi Rui TAN:** Data curation, Writing – original draft, Writing – review & editing. **Shijia CHAN:** Supervision, Writing – review & editing.

Conflicts of interest statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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