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# COVID-19-related adrenal haemorrhage: Multicentre UK experience and systematic review of the literature

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## Abstract

**Objective:** Adrenal haemorrhage (AH) is an uncommon, usually incidental imaging finding in acutely unwell patients. AH has been reported during coronavirus disease 2019 (COVID-19) infection and following ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccination. The Society for Endocrinology (SfE) established a task force to describe the UK experience of COVID-19-related AH.

**Design:** A systematic literature review was undertaken. A survey was conducted through the SfE clinical membership to identify patients with COVID-19-related AH using a standardized data collection tool.

**Results:** The literature search yielded 25 cases of COVID-19-related AH (19 bilateral; 13 infection-related, and 12 vaccine-related). Eight UK centres responded to the survey with at least one case. A total of 18 cases were included in the descriptive study, including 11 from the survey and 7 UK-based patients from the systematic review. Seven patients (4 males; median age 53 (range 26–70) years), had infection-related AH (four bilateral). Median time from positive COVID-19 test to AH detection was 8 (range 1–30) days. Eleven cases of vaccine-related AH (eight bilateral) were captured (3 males; median age 47 (range 23–78) years). Median time between vaccination (nine Oxford-AstraZeneca and two Pfizer-BioNTech) and AH was 9 (range 2–27) days; 9/11 AH occurred after the first vaccine dose. Acute abdominal pain was the commonest presentation (72%) in AH of any cause. All 12 patients with bilateral AH and one patient with unilateral AH required glucocorticoid replacement.

**Conclusion:** Adrenal haemorrhage with consequential adrenal insufficiency can be a complication of COVID-19 infection and vaccination. Adrenal function assessment is mandatory to avoid the potentially fatal consequences of unrecognized adrenal insufficiency.

KEYWORDS

adrenal apoplexy, adrenal infarction, adrenal insufficiency, COVID-19 vaccine, SARS-CoV-2

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## 1 | INTRODUCTION

Adrenal haemorrhage (AH) is a heterogeneous condition that is most frequently detected incidentally on abdominal imaging in acutely unwell or trauma patients. It is considered uncommon but is likely underrecognized as no clinical features can immediately alert to the diagnosis.[1] Several risk factors are associated with an increased risk of atraumatic AH including underlying adrenal tumour, sepsis, and adrenal vein thrombosis.[2] Whereas unilateral AH can be clinically silent, bilateral AH leads to adrenal insufficiency in as many as 100% of patients[3] with the risk of fatal adrenal crisis without prompt recognition and glucocorticoid treatment.

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is predominantly a respiratory illness but can also be associated with extra-pulmonary manifestations, that include the endocrine system.[4] Thrombotic complications are common during a COVID-19 illness, linked to the dramatic cytokine response; these occur in 9.5% of all patients [5] and up to 31% of patients in an intensive care setting.[6] Several vaccines against SARS-CoV-2 have been approved, with one of the most widely administered being the adenoviral vector-based ChAdOx1 nCoV-19 (Oxford-AstraZeneca). Shortly after rollout, concerns developed regarding a rare risk of thrombocytopenia and thrombosis among people who received the Oxford-AstraZeneca vaccine; a phenomenon subsequently termed vaccine-induced immune thrombocytopenia and thrombosis (VITT).[7]

We encountered patients identified to have unilateral or bilateral AH during COVID-19 illness or following the Oxford-AstraZeneca vaccine in the context of VITT. Indeed, in the last two years, an increasing number of case reports have emerged in the literature (see Table 1 for references). In response, the Society for Endocrinology established a task force to describe the United Kingdom's experience of COVID-19-related AH with the aim to improve awareness and rapid diagnosis of this potentially life threatening COVID-19 complication.

## 2 | METHODS

### 2.1 | Overview of the literature

To assess the international experience of COVID-19-related AH, a systematic review of the literature was undertaken. Systematic Ovid Medline search using the keywords "adrenal adj3 h?emorrhag*" AND "COVID-19" combined with the MeSH terms "adrenal gland diseases" AND "haemorrhage" AND "COVID-19". Ovid Embase search using the keywords "adrenal adj3 h?emorrhag*" AND "COVID-19". The search period was 1 January 2020 to 15 June 2022. Case reports in conference proceedings have also been considered. Two members of the task force independently identified the case reports of COVID-19 infection or COVID-19 vaccine-related AH. The complete list of identified reports is summarized in Table 1.

### 2.2 | Design of the United Kingdom national survey and data collection

The task force consisted of endocrinologists and a haematologist with expertise in thrombotic disorders. A survey was designed by the task force with the purpose of identifying specialists and centres that encountered patients with diagnosed AH during COVID-19 illness or following the Oxford-AstraZeneca vaccine in the context of VITT. An invitation to participate was emailed to the Society for Endocrinology UK clinical membership and separately to 150 clinical leads of endocrinology departments across the country between February and July 2022. Timelines to express an interest to participate in the survey were defined. Clinicians who responded to the survey and expressed their interest in the following national audit aimed to collect data regarding the presentation of patients with COVID-19 illness- or vaccine-related AH via a standard anonymized data capture EXCEL sheet that they completed and returned to the task force, adhering to the Caldicott Principles.

### 2.3 | Definition of COVID-19 illness- or vaccine-related adrenal haemorrhage

AH was defined as potentially COVID-19 illness-related if the patient had a positive PCR test within 30 days before the detection of the adrenal abnormality. AH was defined as COVID-19 vaccine-related if the adrenal mass was detected 5–30 days after receiving a COVID-19 vaccine.[7] For the diagnosis of VITT, the Expert Haematology Panel's case definition criteria were used, whereby VITT was classified as 'definite', 'probable', 'possible', or 'unlikely'. VITT was considered definite if symptom onset occurred 5–30 days post-COVID-19 vaccination, in the presence of thrombosis, thrombocytopenia (platelet count $< 150 \times 10^9$/L), D-Dimer > 4000 μ/mL, and positive antiplatelet factor 4 antibodies,[7] and probable if only four of these criteria were fulfilled.

### 2.4 | Data collection and interpretation

The requested data included: age of patients at diagnosis of AH, gender, COVID-19 PCR test result (if applicable), type of COVID-19 vaccine received and date of administration (if applicable), laterality of AH (right, left, or bilateral), radiological characteristics of the haematoma (size of haematoma, contrast enhancement and density on computerized tomography (CT), magnetic resonance imaging (MRI) characteristics, presence of surrounding soft tissue stranding or retroperitoneal haematoma), presence of other risk factors for haemorrhage (such as anticoagulants use or coagulopathy, underlying adrenal tumour), clinical features (such as asymptomatic, abdominal pain, fever, and hypotension), laboratory investigations (blood counts, clotting profile, platelet factor-3 ELISA, cortisol, renin, and aldosterone), presence of extra-adrenal thrombosis, details on treatment received, and adrenal function and medications taken at last follow

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**TABLE 1** Case reports of COVID-19-related adrenal haemorrhage or infarction.

| COVID-19 infection-related adrenal haemorrhage or infarction | | | | |
|---|---|---|---|---|
| **Authors** | **Month/year of publication** | **City, Country** | **Sex/age (in years)** | **Unilateral or bilateral haemorrhage or infarction** |
| Rebollo-Román et al. | September 2021 | Córdoba, Spain | M/62 | Left adrenal haemorrhage – underlying phaeochromocytoma, previously unknown |
| Miranda R et a. | July 2021 | Santiago, Chile | M/47 | Bilateral haemorrhage |
| Machado I et al. | July 2021 | Sao Paolo, Brazil | F/46 | Bilateral infarction |
| Asano Y et al. | June 2021 | Nagano, Japan | F/76 | Bilateral infarction |
| Sreedharan R et al. | March 2021 | Ohio, USA | Unavailable | Bilateral haemorrhage |
| Elkhouly M et al. | March 2021 | London, UK | M/50 | Bilateral haemorrhage |
| Jaiswal R and Schulman-Rosenbaum R | 2021 | New York, US | F/71 | Bilateral haemorrhage |
| Shaamile F and O'Halloran DJ | 2021 | Cork, Ireland | M/61 | Right adrenal haemorrhage |
| Haider S et al. | 2021 | Michigan, US | M/71 | Bilateral infarction |
| Kumar R et al. | May 2020 | London, UK | F/70 | Bilateral infarction |
| Sharrack N et al. | November 2020 | Barnsley, UK | M/53 | Right adrenal haemorrhage |
| Frankel M et al. | August 2020 | Jerusalem, Israel | F/66 | Bilateral haemorrhage |
| Alvarez-Troncoso J et al. | 2020 | Madrid, Spain | M/70 | Bilateral haemorrhage |

| COVID-19 vaccine-related adrenal haemorrhage or infarction | | | | | | |
|---|---|---|---|---|---|---|
| **Authors** | **Month/year of publication** | **Hospital, City, Country** | **Sex/age (in years)** | **Unilateral or bilateral haemorrhage** | **Type of vaccine** | **Time interval since the vaccine (in days)** |
| Efthymiadis A et al | June 2022 | Oxford, UK | F/23 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 8 |
| Tews H et al. | April 2022 | Regensburg, Germany | M/39 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 10 |
| Graf A et al. (Case 1) | February 2022 | London, UK | M/46 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 8 |
| Graf A et al. (Case 2) | February 2022 | London, UK | F/38 | Left adrenal infarction in the context of VITT | AstraZeneca | 11 |
| Tha T et al. | December 2021 | Birmingham, UK | F/47 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 8 |
| Varona J et al. | September 2021 | Madrid, Spain | M/47 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 10 |
| Douxfils J et al | August 2021 | Namur, Belgium | F/83 | Right adrenal haematoma and left adrenal infarction in the context of VITT | AstraZeneca | 14 |



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TABLE 1 (Continued)

| COVID-19 vaccine-related adrenal haemorrhage or infarction | | | | | | |
|---|---|---|---|---|---|---|
| Authors | Month/year of publication | Hospital, City, Country | Sex/age (in years) | Unilateral or bilateral haemorrhage | Type of vaccine | Time interval since the vaccine (in days) |
| Taylor P et al. | June 2021 | Cardiff, UK | M/38 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 8 |
| Blauenfeldt et al. | April 2021 | Aarhus, Denmark | F/60 | Bilateral haemorrhage in the context of VITT | AstraZeneca | 7 |
| D'Agostino V et al. | April 2021 | Naples, Italy | F/54 | Bilateral haemorrhage in the context of VITT | Astrazeneca | 12 |
| Boyle L et al. | 2021 | London, UK | F/55 | Left adrenal haemorrhage | AstraZeneca | 8 |
| Sabahat et al. | 2021 | Slough, UK | F/23 | Bilateral haemorrhage in the context of probable VITT | AstraZeneca | 10 |

up. Information about previous publication in a peer-reviewed journal or conference proceedings were also requested.

All the provided data were collated, and data consistency was verified by at least two members of the task force. Inconsistencies and incomplete data were raised with the local endocrinologists by specific queries until they were subsequently resolved.

The same clinical, radiological, biochemical and outcome data as above were extracted from the case reports available in the literature from UK-based centres that were not captured through the survey.

Final data were evaluated to highlight differences and similarities in terms of demographics, presentation, and clinical outcome of patients with COVID-19 illness- or vaccine-related AH.

### 2.5 | Statistical analysis

This is a descriptive study, and therefore no statistical analysis was involved. Wherever relevant, data are presented as median and range.

## 3 | RESULTS

### 3.1 | Overview of the literature

Our search identified a total of 25 cases of COVID-19-related AH (Figure 1). In particular, these included 9 cases of AH[8–17] and four cases of adrenal infarction[18–21] in the context of COVID-19 infection. All four cases of adrenal infarction were bilateral, with no radiological features of haemorrhage, while 6/9 cases of AH were bilateral (66%) with three unilateral (2 left and 1 right sided). The median age of the patients with COVID-19 infection-related AH or adrenal infarction was 64 years (range 46–76). The sex distribution was near equal with seven males and five females (excluding one case where sex was unknown).

Moreover, 12 cases[22–32] of AH following COVID-19 vaccination were identified. Eight (66.7%) of the reported cases were females, and median age was 46 years (range 23–83). All reported cases presented 7–12 days following COVID-19 AstraZeneca vaccination. Most cases (9/12) presented with bilateral AH (75%).

Of note, 10 of the 26 cases identified through the literature search originated from the UK (three COVID-19 infection-related and seven vaccine-related). A full description of available data from published reports is reported in Table 1.

### 3.2 | Overview of the survey and descriptive study

Eight UK centres reported encountering patients that met the definition criteria of COVID-19-related AH, while six centres replied that no such cases were faced. Overall, the survey returned 11 patients that met the definition criteria above for COVID-19-related AH. For a comprehensive overview, we also included 7 of the 10

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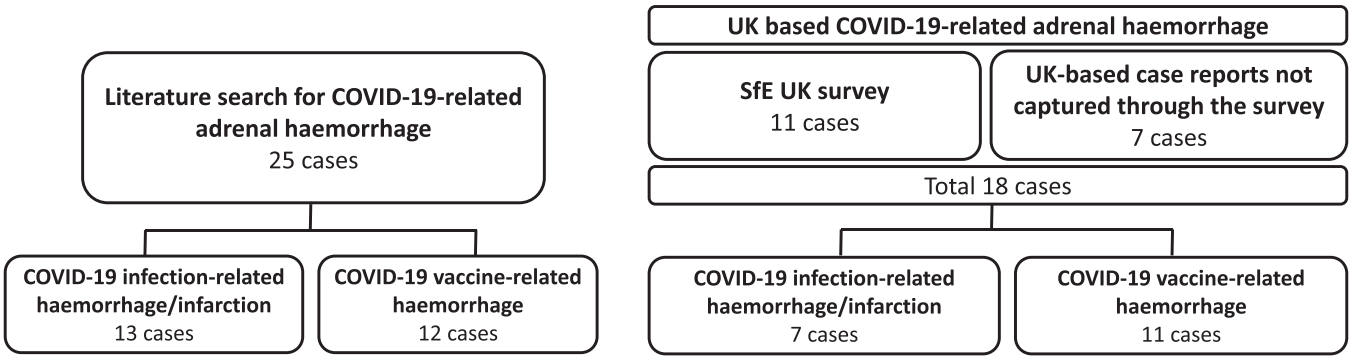



**FIGURE 1** An outline of the number of pateints identified through the systematic literature search and the UK survey and the cohort of patients included in the descriptive study. COVID-19, coronavirus disease 2019.

UK-based patients from the systematic review, who were not captured through the survey resulting in a total of 18 cases (Figure 1). The details regarding the patient's demographic and clinical characteristics, the clinical presentation, and the outcome are reported in Tables 2–4, respectively.

## 3.3 | COVID-19 infection-related adrenal haemorrhage

We identified seven patients (four men and three women) with COVID-19 infection-related AH (Table 2). The median age was 53 years (range 26–70). Four patients had bilateral AH (57%); diameters of adrenal haematoma/abnormality ranged from 42 mm to 125 mm. All patients had positive COVID-19 PCR tests and CT scan was initially undertaken to evaluate clinical deterioration. The median duration between the positive COVID-19 PCR test and radiological detection of AH was 8 days (range 1–30). Two patients (one bilateral and one unilateral AH) had associated pulmonary embolism and one (bilateral AH) had lower limb deep vein thrombosis.

Among the four patients with bilateral AH, two had other risk factors for haemorrhage, that is, one patient was on low molecular weight heparin, and another was known to have an underlying unilateral nonfunctioning adrenal adenoma. Moreover, three of them (75%) presented with acute abdominal pain whilst in one case the detection of AH was incidental on imaging undertaken to exclude pulmonary embolism (Table 3). Hypotension was evident in 50% of patients with bilateral AH and hyponatraemia occurred in another 50%. In two patients with bilateral AH, random cortisol levels were considered reassuring being 734 nmol/L and 625 nmol/L and therefore patients were not treated with glucocorticoids. In the other two patients with bilateral AH, the random cortisols were considered inconclusive at 458 nmol/L and 215 nmol/L and as the patients were symptomatic with hypotension and tachycardia, glucocorticoid, and mineralocorticoid replacement was commenced. One glucocorticoid-treated patient with bilateral AH subsequently failed an ACTH stimulation test (baseline cortisol 242 nmol/L; 30-min cortisol 264 nmol/L) and died of COVID-19 pneumonitis. The second glucocorticoid-treated patient subsequently passed an ACTH stimulation test (baseline cortisol, 171 nmo/L; 30-min cortisol 458 nmol/L) and hydrocortisone and fludrocortisone were discontinued. One nonglucocorticoid treated patient died of massive pulmonary embolism (Table 4).

Unilateral AH was diagnosed incidentally in all three patients (two right sided and one left sided) who underwent imaging to evaluate COVID-19 chest infection or to exclude pulmonary embolism (Tables 2 and 3). One patient was pregnant at the time of the diagnosis of AH and had a previously unknown underlying indeterminate nonfunctioning adrenal tumour, but the other two had no identifiable risk factors for haemorrhage. None of the patients with unilateral AH presented with abdominal pain or hypotension, or had adrenal insufficiency based on cortisol assessments that were considered reassuring or no assessment was undertaken as adrenal insufficiency was not suspected.

## 3.4 | COVID-19 vaccine-related adrenal haemorrhage

We uncovered 11 cases of COVID-19 vaccine-related AH, eight of whom were women (Table 2). The median age of patients was 47 years (range 23–78). Most patients had bilateral AH ($N = 8$; 73%). The size of AH ranged from 30 mm to 89 mm. In nine patients, AH followed Oxford-AstraZeneca vaccine administration (82%) while in two cases AH was associated with the Pfizer-BioNTech mRNA vaccine. The median time between the receipt of vaccine and detection of AH was 9 days (range 2–27). AH was reported in association with the first dose of the vaccine in nine patients (82%; eight Oxford-AstraZeneca vaccine and one Pfizer-BioNTech), one case (Pfizer-BioNTech) followed the second dose, and one (Oxford-AstraZeneca) followed booster dosing. At the time of AH detection, 27% ($N = 3$) of patients were taking anti-coagulants (two on apixaban and one edoxaban), one of whom had bilateral AH on a background of bilateral adrenal adenomas. Another patient with unilateral AH showed fluorodeoxyglucose avid uptake at PET-CT scan suggestive of an underlying adrenal tumour. Otherwise, no pre-existing risk

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**TABLE 2** Characteristics of 18 UK patients with adrenal haemorrhage (AH) related to COVID-19 infection or vaccination.

| Case | Centre | Publication status | Infection or vaccine-related | Days after PCR + or vaccine | Type of vaccine | Dose | Sex | Age | Unilateral/ bilateral AH | Maximum size of AH on imaging (mm) | Radiological characteristics | Extra-adrenal thrombosis | Risk factors |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | University Hospitals Birmingham NHS Foundation Trust | Submitted | Infection | 15 | NA | NA | F | 26 | Unilateral - left | 125 | Indeterminate lesion (heterogeneous) | No | None (adrenal tumour diagnosed later) |
| 2 | St George's University Hospitals NHS Foundation Trust | Unpublished | Infection | 35 | NA | NA | M | 39 | Bilateral | Unknown | Haziness with bulky adrenals | No | None |
| 3 | St George's University Hospitals NHS Foundation Trust | Unpublished | Infection | 8 | NA | NA | F | 61 | Unilateral - right | Unknown | Fluid around right kidney | No | Unknown |
| 4 | Salisbury NHS Foundation Trust | Unpublished | Infection | 12 | NA | NA | M | 77 | Bilateral | 68 | Hyperdense content (HU 60-65) | Yes (PE) | Heparin use |
| 5 | Mid and South Essex NHS Foundation Trust | Published in journal[12] | Infection | 1 | NA | NA | M | 50 | Bilateral | Unknown | Unknown | Yes (deep venous thrombosis) | History of adrenal tumour |
| 6 | Barnsley Hospital NHS Foundation Trust | Published in journal[15] | Infection | 1 | NA | NA | M | 50 | Unilateral - right | 12 | Heterogeneous lesion, surrounding soft tissue | Yes (PE) | None |
| 7 | London North West University Healthcare NHS trust | Published in journal[21] | Infection | 1 | NA | NA | F | 70 | Bilateral | Unknown | Enlarged adrenals, | Unknown | None |

(Continues)



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**TABLE 2** (Continued)

| Case | Centre | Publication status | Infection or vaccine-related | Days after PCR + or vaccine | Type of vaccine | Dose | Sex | Age | Unilateral/ bilateral AH | Maximum size of AH on imaging (mm) | Radiological characteristics | Extra-adrenal thrombosis | Risk factors |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | The Princess Alexandra Hospital NHS Trust | Unpublished | VITT-definite | 9 | AZ | First | F | 47 | Bilateral | Unknown | Hyperdense content (HU 58) | Yes (PE) | None |
| 9 | University Hospital of Wales | Published in journal[29] | VITT-definite | 8 | AZ | First | M | 38 | Bilateral | Unknown | Retroperitoneal fat stranding, fluid around adrenals | Yes (PE + CVST) | None |
| 10 | University Hospital of Wales | Unpublished | VITT-unlikely | 27 | Pfizer | Second | M | 73 | Unilateral - left | Unknown | High density lesion with retro-peritoneal fat stranding | Yes (CVST) | None |
| 11 | Oxford University Hospitals NHS Trust | Published in journal[22] | VITT-definite | 16 | AZ | First | F | 23 | Bilateral | 48 | MRI T2 low signal lesions | Yes (PE + splenic vein thrombosis) | Anticoagulant use |
| 12 | The Leeds Teaching Hospitals NHS Trust | Unpublished | VITT-unlikely | 20 | Pfizer | First | F | 78 | Unilateral - right | 70 | AH with abnormal FDG avid soft tissue, suggestive of underlying tumour | No | None |
| 13 | Chelsea and Westmin-ster Hospital NHS Foundation Trust | Published in conference pro-ceedings[32] | VITT-Probable | 8 | AZ | First | F | 55 | Bilateral | 35 | Bilateral hyperplasia | Yes (PE + ovary) | None |
| 14 | University Hospitals of Leicester NHS Trust | Unpublished | VITT-possible | 2 | AZ | Booster | F | 70 | Bilateral | 100 | Periadrenal and perinephric stranding | No | Anticoagulant use + history of bilateral adrenal adenomas |



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**TABLE 2** (Continued)

| Case | Centre | Publication status | Infection or vaccine-related | Days after PCR + or vaccine | Type of vaccine | Dose | Sex | Age | Unilateral/ bilateral AH | Maximum size of AH on imaging (mm) | Radiological characteristics | Extra-adrenal thrombosis | Risk factors |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | University College London Hospitals NHS Foundation Trust | Published in journal[25] | VITT-definite | 8 | AZ | First | M | 46 | Bilateral | Unknown | Surrounding soft tissue stranding | Yes (acute MI, occipital infarction, dural CVST, PE, portal and hepatic vein thrombosis, bilateral renal cortical infarcts) | None |
| 16 | University College London Hospitals NHS Foundation Trust | Published in journal[25] | VITT-definite | 11 | AZ | First | F | 38 | Unilateral - left | Unknown | | No | None |
| 17 | Sandwell and West Birmingham Hospitals NHS Trust | Published in journal[26] | VITT-definite | 8 | AZ | First | F | 47 | Bilateral | Unknown | Hyperdense content (HU 54) | Yes (PE + renal infarcts) | None |
| 18 | Wexham Park Hospital | Published in conference pro-ceedings[24] | VITT-probable | 10 | AZ | First | F | 23 | Bilateral | Unknown | Surrounding soft tissue stranding | Yes (CVST, splenic vein, right ventricle) | Anticoagulant use |

Abbreviations: AZ, Astra Zeneca; CVST, cerebral venous sinus thrombosis; NA, not applicable; PE, pulmonary embolism, risk factors: heparin or anti-coagulant drug use, history of an adrenal tumour, anti-phospholipid syndrome.



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**TABLE 3** Presentation of 18 UK patients with adrenal haemorrhage (AH) related to COVID-19 infection or vaccination.

| Case | Type of AH | Later AH | Symptoms/signs | Sodium/potassium (mmol/L) | D-dimer | Fibrinogen (g/L) | PF4 ELISA antibody | Morning cortisol (nmol/L) | Cortisol peak at stimulation test (nmol/L) | Adrenal insufficiency | Replacement treatment given |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Infection | Unilateral | Abdominal pain | Unknown | Unknown | Unknown | NA | 209 | Not done | No | No |
| 2 | Infection | Bilateral | Abdominal pain, Hypotension, Vomiting, Tachycardia | 141/4.1 | Unknown | 7.6 | NA | Unknown | 458 | Yes | Yes (HC + FC) |
| 3 | Infection | Unilateral | Unknown | Unknown | Unknown | Unknown | NA | Unknown | Unknown | Unknown | Unknown |
| 4 | Infection | Bilateral | Hypotension, Tachycardia | 126/5.5 | 670 | 5.3 | NA | Unknown | 264 | Yes | Yes (HC + FC) |
| 5 | Infection | Bilateral | Abdominal pain, fever | 135/3.9 | 10613 | Unknown | NA | Unknown | Unknown | No (random cortisol >700) | No |
| 6 | Infection | Unilateral | Fever | Unknown | 3.9 | 7.75 | NA | Unknown | Unknown | No (random cortisol >600) | No |
| 7 | Infection | Bilateral | Abdominal pain, fever | 112/unknown | Unknown | Unknown | NA | Unknown | Unknown | No (random cortisol >600) | No |
| 8 | VITT-definite | Bilateral | Abdominal pain, Fatigue, Vomiting | 138/3.9 | 24004 | 4.2 | Positive | 32 | 30 | Yes | Yes (HC + FC) |
| 9 | VITT-definite | Bilateral | Abdominal pain, Headache | 136/3.6 | >20000 | 3.5 | Positive | 61 | Not done | Yes | Yes (HC + FC) |
| 10 | VITT-unlikely | Unilateral | Abdominal pain | 135/4.1 | 3467 | 4 | Not done | Long-term prednisolone | Long-term prednisolone | Long-term prednisolone | Long-term prednisolone |
| 11 | VITT-definite | Bilateral | Headache, confusion, Fever, Hypotension, Seizures, Tachycardia | 132/4 | >100000 | Unknown | Positive | 25 | Not done | Yes | Yes (HC + FC) |
| 12 | VITT-unlikely | Unilateral | None | 133/4.8 | Not done | >4.5 | Unknown | Unknown | Unknown | Unknown | No |
| 13 | VITT-probable | Bilateral | Abdominal pain, Vomiting, Lethargy, Tachycardia | 130/3.3 | 8099 | 6.98 | Not done | 151 | 157 | Yes | Yes (HC) |
| 14 | VITT-possible | Bilateral | Abdominal pain, Hypotension | 135/4.4 | Unknown | 6.7 | Not done | Not done | Unknown | Not assessed | Yes (HC + FC) |

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**TABLE 3** (Continued)

| Case | Type of AH | Later AH | Symptoms/signs | Sodium/potassium (mmol/L) | D-dimer | Fibrinogen (g/L) | PF4 ELISA antibody | Morning cortisol (nmol/L) | Cortisol peak at stimulation test (nmol/L) | Adrenal insufficiency | Replacement treatment given |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | VITT-definite | Bilateral | Abdominal pain, Vomiting | Unknown | >80000 | Unknown | Positive | 16 | 17 | Yes | Yes (HC + FC) |
| 16 | VITT-definite | Unilateral | Abdominal pain, Headache, Vomiting | Unknown | 4160 | Unknown | Positive | 187 | 239 | Yes | Yes (HC) |
| 17 | VITT-definite | Bilateral | Abdominal pain, Vomiting | Unknown | 24000 | 4.2 | Positive | Unknown | Failed | Yes | Yes (HC + FC) |
| 18 | VITT-probable | Bilateral | Abdominal pain, Headache, Tachycardia | Unknown | 10000 | Unknown | Not done | 25 | Unknown | Yes | Yes (HC) |

Abbreviations: COVID-19, coronavirus disease 2019; FC, fludrocortisone; HC, hydrocortisone; NA, not applicable; PF4, platelet factor; SST, Short Synacthen Test

factors for AH were observed. Regarding the diagnosis of VITT, six patients were definite, two probable, one possible and two unlikely (Pfizer-BioNTech). Six patients had associated pulmonary embolism, four had cerebral venous sinus thrombosis, and other sites of thrombosis included cardiac ventricles (two patients), splenic vein (two patients), renal infarcts (two patients), and portal, hepatic and ovarian veins (one patient each).

Bilateral AH was always associated with the Oxford-AstraZeneca vaccine. Seven patients (88%) presented with acute abdominal pain and in one patient imaging was undertaken to re-evaluate pulmonary embolism (Table 3). Two patients with bilateral AH (25%) had hypotension, and none had hyponatraemia. In the acute setting, 5 patients with bilateral AH (63%) had very low cortisol levels ranging from undetectable to 87 nmol/L, and therefore glucocorticoid and mineralocorticoid replacement were commenced. Three patients were empirically treated with glucocorticoids before their adrenal function was checked, with the later addition of mineralocorticoids; two subsequently failed their ACTH stimulation test and one is awaiting further investigations. Two patients had ACTH stimulation tests during follow up which showed suboptimal response (Table 4).

Two of the three patients with unilateral AH received the Pfizer-BioNTech vaccine, 20 and 27 days beforehand (Table 2). In two patients, AH was left sided and one right sided. Two patients presented with acute abdominal pain whilst in the third the detection of haemorrhage was incidental; none had hypotension or electrolyte disturbance (Table 3). One patient had associated cerebral venous sinus thrombosis. One patient (presented with abdominal pain and vomiting) had adrenal insufficiency confirmed by an ACTH stimulation test, another was on long-term prednisolone, and the third patient was not treated with glucocorticoids and did not undergo adrenocortical function testing (Table 4).

## 4 | DISCUSSION

This survey describes the largest data set thus far characterizing patients with COVID-19-related AH. Early studies suggested that AH is an underrecognized entity as the incidence in autopsy of patients died in shock was 15%[33] compared with 0.14%–1.8% in unselected autopsies.[34,35] One cannot infer the incidence of AH from these data as the numerator is minute compared to a denominator of millions of people who contracted the COVID-19 infection and received the vaccines. However, these data enable us to make useful observations for clinicians in guiding timely recognition and treatment that may prevent fatal adrenal crisis.

The vascular structure of the adrenal glands makes them susceptible to turbulent flow or stasis due to their abundant arterial supply with relatively limited drainage via a single vein.[36] This so-called "adrenal dam" renders the adrenal gland highly susceptible to haemorrhage in any pro-thrombotic state, with adrenal vein thrombosis the likely primary event. COVID-19 illness represents a prothrombotic state in many cases[5,6] which may predispose to haemorrhage, though sepsis also increases the risk of AH by

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**TABLE 4** Outcome at follow-up of 18 UK patients with adrenal haemorrhage (AH) related to COVID-19 infection or vaccination.

| Case | Type of AH | Unilateral/ bilateral AH | Duration of hospital stay (days) | Outcome at last follow-up | Cause of death | Adrenal function re-tested | Morning cortisol (nmol/L) | Cortisol peak at SST (nmol/L) | Adrenal insufficiency | Radiological follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Infection | Unilateral | | Alive | NA | Yes -baseline | | Not done | No | Yes – underlying adrenal tumour |
| 2 | Infection | Bilateral | 7 | Alive | NA | Yes - SST | 171 | 458 | | - |
| 3 | Infection | Unilateral | Unknown | Unknown | NA | Unknown | Unknown | Unknown | Unknown | Unknown |
| 4 | Infection | Bilateral | 86 | Deceased | COVID-19 pneumonitis | No | - | - | - | - |
| 5 | Infection | Bilateral | 5 | Deceased | Massive pulmonary embolism | No | - | - | - | - |
| 6 | Infection | Unilateral | 7 | Alive | NA | Yes - SST | 400 | 812 | No | Yes |
| 7 | Infection | Bilateral | Unknown | Alive | NA | Unknown | Unknown | Unknown | Unknown | Unknown |
| 8 | VITT-definite | Bilateral | 16 | Alive | NA | No | - | - | - | - |
| 9 | VITT-definite | Bilateral | 17 | Alive | NA | Yes - SST | 141 | 139 | Yes | - |
| 10 | VITT-unlikely | Unilateral | 5 | Alive | NA | Yes - SST | 145 | 385 | Yes | - |
| 11 | VITT-definite | Bilateral | 14 | Alive | NA | Yes - SST | 37 | 43 | Yes | - |
| 12 | VITT-unlikely | Unilateral | 0 | Alive | NA | No | - | - | - | - |
| 13 | VITT-probable | Bilateral | 27 | Alive | NA | No | - | - | - | - |
| 14 | VITT-possible | Bilateral | 6 | Alive | NA | No | - | - | - | - |
| 15 | VITT-definite | Bilateral | 23 | Alive | NA | No | - | - | - | Yes |
| 16 | VITT-definite | Unilateral | Unknown | Alive | NA | No | - | - | - | Yes |
| 17 | VITT-definite | Bilateral | Unknown | Alive | NA | No | - | - | - | Unknown |
| 18 | VITT-probable | Bilateral | Unknown | Alive | NA | No | - | - | - | Unknown |

Abbreviation: COVID-19, coronavirus disease 2019.



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six-fold.[37] Adrenal vein thrombosis was evident in 6 out of 220 (3%) VITT patients in the UK [7] and associated with thrombosis in other sites.

Although there was no predilection to either sex in COVID-19 infection-related AH, most patients with vaccine-related haemorrhage were women (73% in the UK survey and 67% in the systematic review). This female predilection has previously been highlighted,[38] although the cause is unclear. Noteworthy, VITT-related AH was always associated with the first dose of Oxford-AstraZeneca vaccine.

Most patients (72%) underwent imaging for acute abdominal pain which was commoner with bilateral, compared with unilateral AH. Therefore, during the COVID-19 pandemic and as the vaccines roll out continues, it is important to consider AH in the differential diagnosis of acute abdominal pain, particularly in the context of VITT.

As expected, adrenal insufficiency was more evident in bilateral AH but also reported in unilateral AH associated with VITT. Adrenal insufficiency following unilateral AH has previously been observed,[2,39,40] likely suggesting microinfarction in the contralateral adrenal gland. Therefore, in bilateral AH, glucocorticoid treatment should be commenced without delay whilst clinicians should have a low threshold to start treatment in patients with unilateral AH, if they display features of adrenal insufficiency. Adrenal function testing should be undertaken when patients are stable, ideally in an outpatient setting. It is important to recognize that the rapidity of haemorrhage and primary adrenal insufficiency may not allow sufficient time for skin hyperpigmentation to manifest.

Patients with COVID-19 infection-related AH presented with more clinical manifestations of adrenal insufficiency (hypotension), compared to AH that followed vaccination, likely due to the added stress of the infection and cytokine storm. Furthermore, two patients with COVID-19 infection-related AH died while no death was recorded in the captured patients with vaccine-related AH. Of relevance, AH has been associated with poor clinical outcomes in patients with sepsis for possibly being a marker of severe physiological stress.[2,41]

Most patients in this study did not have other identifiable risk factors for AH. When AH is detected, it is important to exclude an underlying adrenal tumour as outside of the context of COVID-19 half of haemorrhagic adrenal masses turn out to be phaeochromocytomas, and 20% are malignancy-related.[42] Therefore, a period of radiological surveillance is usually required to ensure the resolution of haematoma.[1]

There is a paucity of data that studied the natural history of primary adrenal insufficiency from AH, however, recovery of adrenal function was uncommonly observed in case series.[2,3,43]

The survey identified two patients who developed adrenal haemorrhage in the days following the Pfizer-BioNTech mRNA-based vaccine. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) received reports of AH and thrombocytopenia following vaccination with Pfizer-BioNTech and Moderna. As mRNA-based vaccine will dominate future vaccine development, it remains important to be alert to this possible association.

More generally, as AH has no specific clinical features, vigilance is key to suspect the diagnosis in acutely unwell patients, particularly in prothrombotic and florid infective states.

The strengths of our study include the comparatively large number of cases reported, with data collection undertaken systematically after a widely circulated survey. However, our study was limited by the retrospective nature of the data collection and lack of long-term follow-up. Finally, whilst we highlight the importance of timely recognition and treatment of AH in relation to COVID-19 vaccination, it is crucial to emphasize that this complication appears to be rare. In the UK, the competent authority, MHRA, concluded that the benefits of the Oxford-AstraZeneca vaccine far outweigh any potential risks.[44]

## 5 | CONCLUSION

AH can be a serious complication of COVID-19 infection and vaccination. Adrenal insufficiency is present in most cases of bilateral AH and can occur in unilateral adrenal haemorrhage associated with VITT. A high index of suspicion for AH is required, particularly in the presence of unexplained abdominal pain, to avoid the potentially fatal consequences of unrecognised adrenal insufficiency.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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