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# The Diagnoses and Outcomes of Emergency Patients With an Elevated D-Dimer Over the Next 90 Days

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## ABSTRACT

**BACKGROUND:** It is not known what diagnoses are associated with an elevated D-dimer in unselected patients attending emergency departments (ED), nor have their associated outcomes been determined.

**METHODS:** This was a prospective observational study of 1612 unselected patients attending a Danish ED, with 100% follow-up for 90 days after presentation.

**RESULTS:** The 765 (47%) ED patients with an elevated D-dimer level (ie,  $\geq 0.5$  mg/L) were more likely to be admitted to hospital ( $P < .0001$ ), re-present to health services ( $P = .02$ ), and die within 90 days (8.1% of patients,  $P < .0001$ ). Only 10 patients with a normal D-dimer level (1.2%) died within 90 days. Five had chronic obstructive pulmonary disease and infection, and 5 had cancer (4 of whom also had infection). Venous thromboembolism, infection, neoplasia, anemia, heart failure, and unspecified soft tissue disorders were significantly associated with an elevated D-dimer level. Of the 72 patients with venous thromboembolism, 20 also had infection, 8 had cancer, and 4 had anemia. None of the patients with heart failure, stroke, or acute myocardial infarction with a normal D-dimer level died within 90 days.

**CONCLUSIONS:** In this study, nearly half of all patients attending the ED had an elevated D-dimer level, and these patients were more likely to be admitted to hospital and to re-present to health services or die within 90 days. In this unselected ED patient population, elevated D-dimer levels were found to not only be significantly associated with venous thromboembolism, but to also be associated with infection, cancer, heart failure, and anemia.

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**KEYWORDS:** Cancer; D-dimer; Diagnoses; Infection; Mortality; Prognosis; Unselected emergencies

## INTRODUCTION

Currently the main clinical use of D-dimer is to rule out venous thromboembolism. Elevated D-dimers occur in a variety of clinical scenarios including pneumonia, cardiac

arrest, and cancer.<sup>1-2</sup> D-dimer is a non-specific biomarker that is immediately released by anything that causes the plasmin mediated proteolysis of fibrin<sup>3,4</sup> and has been found to be increased in many conditions presenting to emergency departments.<sup>5,6</sup>

Although not diagnostic for any condition, an elevated D-dimer level is a powerful predictor of mortality. Elevated levels have been independently associated with an increased risk of death from any cause in an apparently healthy adult population.<sup>7</sup> However, it is not known what diagnoses are associated with a positive D-dimer in unselected emergency department (ED) patients, nor the

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outcomes associated with them. There is also concern that D-dimer's routine use as a risk-stratification tool on every ED patient may trigger futile expensive investigations for which there would otherwise be no clinical indication.<sup>8</sup>

This study of unselected patients attending a Danish ED is a secondary analysis of previously published data that showed normal D-dimer levels identified patients at low risk of 30-day mortality.<sup>9</sup> It reports how many patients had an elevated D-dimer at presentation, what diagnoses were associated with elevated levels, and what happened to patients for up to 90 days after presentation.

## MATERIALS AND METHODS

### Study Design

This was a secondary analysis of a prospective observational cohort study performed in an unselected population of adult medical patients attending an ED.<sup>9</sup>

### Setting

This study was conducted at the Hospital of South West Jutland, a 450-bed regional teaching hospital in the region of Southern Denmark that serves approximately 220,000 inhabitants. Medical patients are referred to the ED by general practitioners, outpatient clinics, out-of-hours general practitioner service, and emergency medical services.

### Participants

All non-trauma patients aged 18 years or older who required a blood sample for any clinical indication on arrival to the ED were eligible for inclusion in the study. As D-dimer levels can only be measured up to 10 h after the blood sample is initially collected, the small number of patients who arrived between 10 pm and 1 am could not be included in the study for logistic reasons. Blood tests, other than D-dimer, were requested at the discretion of the treating physician. Participants were asked to provide written informed consent before enrollment. Patients incapable of providing informed consent (eg, language barriers or lacking mental capacity) were excluded. Patients could only be included in the study once, but all the re-presentations to the health service over 90 days after ED presentation were considered. Patients also had to be registered in the Danish healthcare system so that their International Statistical Classification of Diseases, 10th revision (ICD-10) codes and 90-day follow-up data could be obtained.

## Screening and Inclusion

Three trained research assistants performed the screening and inclusion process. All medical patients presenting to the ED between April 24, 2017, and August 19, 2017, were screened for eligibility.

## Data Collection

D-dimers were measured in all included patients. Plasma D-dimer was quantitatively measured using a latex agglutination test (STA Liatest D-dimer, Diagnostica Stago, Asnieres-sur-Seine, France). Citrate plasma for D-dimer estimation was obtained by centrifuging at 3500 rpm for 10 minutes. An elevated D-dimer level was defined as  $\geq 0.5$  mg/L.<sup>10</sup>

## Outcome Ascertainment

The final discharge diagnosis was obtained from the Danish National Patient Registry.<sup>11</sup> The discharge diagnoses of all patients were determined in accordance with the ICD-10 (produced by the World Health Organization).<sup>12</sup> There are more

than 69,800 ICD-10 diagnosis codes, and multiple codes may refer to similar conditions. The codes were, therefore, grouped as follows: All the codes that captured venous thromboembolism and cancer were agreed upon by consensus, arbitrated by an oncologist and angiologist (see [Supplementary Table](#), available online). A list previously published by Vest-Hansen et al<sup>13</sup> was used to identify all ICD-10 codes associated with infection, and the remaining common conditions were identified accordingly: hypertension (ICD10 I10-16), chronic obstructive airway disease (ICD10 J40-47), cerebrovascular disease (ICD10 I60-69), transient ischemic attacks (ICD10 G45), heart failure (ICD10 I50), acute myocardial infarction (ICD10 I21), anemia (ICD10 D50-53,63-64), functional gastrointestinal disorders (ICD10 K59), and unspecified soft tissue disorders (ICD10 M79).

## Blinding

The treating physicians were unaware of the study during its implementation and were only given the D-dimer result if they had ordered it as part of the patients' care. This was done in order to avoid unnecessary investigations and treatment of potential venous thromboembolism that had not been suspected. All results were registered in a confidential research database that could only be accessed by the study investigators after its inclusion phase.

## CLINICAL SIGNIFICANCE

- In this prospective observational study, 47% of patients attending an emergency department had an elevated D-dimer level.
- Patients with elevated D-dimer were more likely to be admitted to hospital and to re-present to health services within 90 days; they were also 7 times more likely to die during this period.
- Elevated D-dimer levels are not only associated with an increased risk for venous thromboembolism, but are also associated with infection, cancer, heart failure, and anemia.

## Ethics

The study design was approved by the Danish Regional Committee of Health Research Ethics (Identifier: S-20170005) and the Danish Data Protection Agency (Identifier: Region Syddanmark 2452). The study protocol was registered at ClinicalTrials.gov on April 3, 2017, before the enrollment of patients (ClinicalTrials.gov, Identifier: NCT03108807). The results are reported in accordance with STROBE guidelines.<sup>14</sup>

## Statistics

Continuous data are presented as median (interquartile range) and categorical data as proportion (95% confidence intervals (CI)). The association between outcome (diagnoses made within 90 days) and D-dimer were presented as unadjusted odds ratios (OR) (95% CI), using Epi Info version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

## RESULTS

During the study period 1612 patients registered in the Danish healthcare system presented to the ED, and 995 (62%) were admitted for a mean length of stay of 4.7 days (standard deviation [SD] = 8.4 days). Patients who were admitted were significantly older than those discharged from the ED (65.9 years [SD 16.9 years] vs 58.1 years [SD 18.7 years];  $P < .0001$ ) and more likely to die within 90 days (6.5 vs 1.1%;  $P < .0001$ ). At the time of presentation, 765 of patients (47%) had a D-dimer level  $\geq 0.5$  mg/L. These patients were older, were assigned more ICD-10 codes, were more likely to be admitted to hospital with a longer length of stay after admission, and more likely to re-present to health services or die within 90 days than those with a D-dimer level  $< 0.5$  mg/L (Table 1).

After discharge from either the ED or the hospital, 601 patients (37%) re-presented to the health services somewhere in Denmark within 90 days. Patients with an elevated D-dimer were 1.29 (95% CI, 1.04-1.58; chi-squared 5.68,  $P = .02$ ) times more likely to re-present, and patients who re-presented were 3.14 (95% CI, 1.86-5.31; chi-squared 21.64;  $P < .00001$ ) times more likely to die within 90 days (Figure).

At the first presentation 5257 ICD-10 codes were recorded (3.3 per patient). Thirty-seven percent were “non-specific factors” (ICD-10 Chapter Z), and 28% were “disorders of the circulation” (ICD-10 Chapter I). Within 90 days of ED presentation, there were only 13 common diagnostic groupings assigned to more than 10 patients. Infection was the most common (24% of patients), followed by hypertension (9% of patients), chronic obstructive pulmonary disease (8% of patients), and neoplasia (7% of patients). Of all the other diagnostic groupings assigned both at presentation and at re-presentation within 90 days, only venous thromboembolism, infection, neoplasia, anemia, heart failure, and unspecified soft tissue disorders were significantly associated with an elevated D-dimer level (Table 2).

Many patients with a raised D-dimer level had more than 1 diagnostic grouping significantly associated with D-dimer elevation. For example, of the 72 patients with venous thromboembolism, 20 also had infection, 8 had cancer, and 4 had anemia (Table 3). Cancer, infection, anemia, and heart failure were all associated with an increased 90-day mortality, whereas venous thromboembolism, regardless of D-dimer, was not (Table 4). Only 10 patients with a normal D-dimer level (mean age = 73.2 years [SD = 10.5 years]) died within 90 days of ED presentation. All of them died between 24 and 73 days after presentation: 5 had chronic obstructive pulmonary disease and infection, and 5 had cancer (4 of whom also had infection). None of the 12 patients diagnosed with venous thromboembolism who had a normal D-dimer level died within 90 days. Nor did any of the patients with heart failure, stroke, or acute myocardial infarction die if their D-dimer level was normal (Table 5).

## DISCUSSION

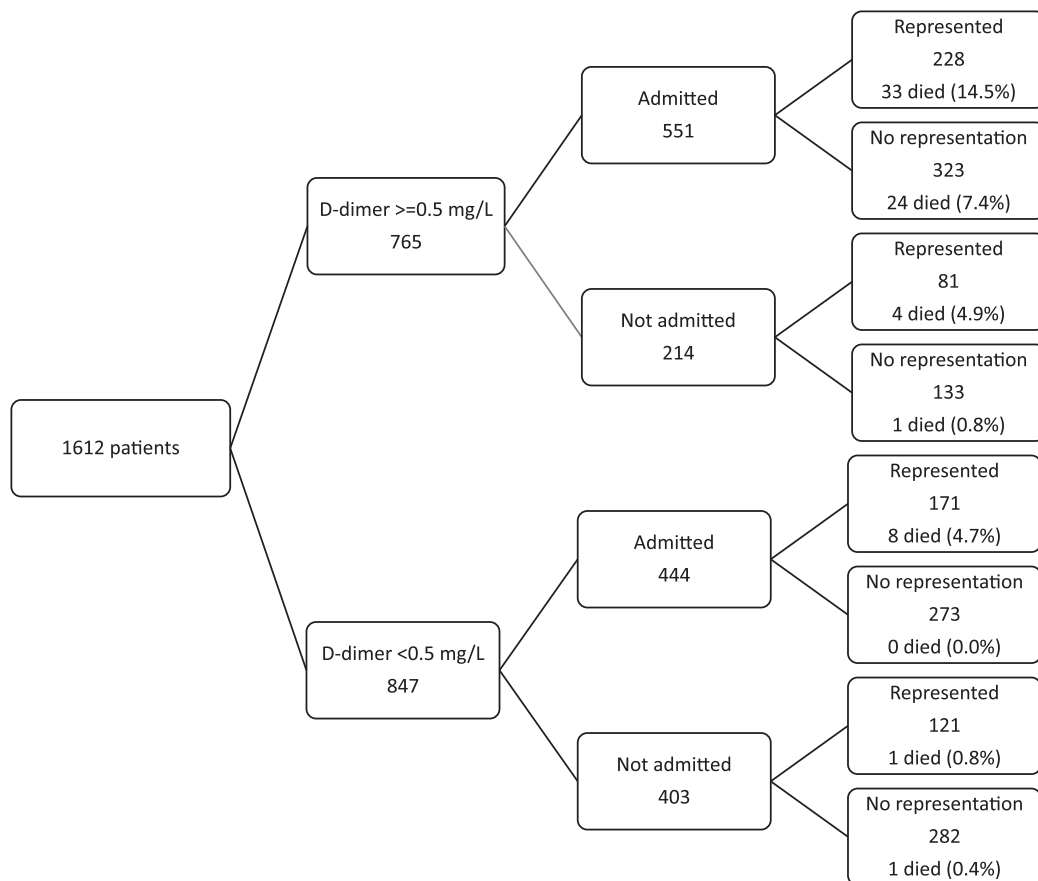
### Main Findings

This study showed that a low D-dimer at presentation to an ED makes death within 90 days, the need for hospital admission, and the chance of subsequent re-presentation unlikely. An elevated D-dimer is associated with 6 diagnostic groupings, which, ranked by prevalence, are infection, neoplasia, venous thromboembolism, anemia, heart failure,

**Table 1** Differences Between Patients Presenting with D-Dimer Levels Above and Below 0.5 mg/L

Variable	D-Dimer $\geq 0.5$ mg/L	D-Dimer $< 0.5$ mg/L	P Value
(n)	765 (47%)	847 (53%)	
Age	68.7 SD 16.2 years	57.7 SD 18.0 years	$< .0001$
Male sex	389 (51%)	423 (50%)	.75
ICD-10 codes assigned at presentation	3.2 SD 2.2	2.5 SD 1.7	$< .0001$
Admitted to hospital	551 (72%)	444 (52%)	$< .0001$
Length of hospital stay if admitted	5.7 SD 8.2 days	3.4 SD 8.4 days	$< .0001$
Re-presented within 90 days	309 (40%)	292 (34%)	.02
Died within 7 days	5 (0.6%)	0 (0.0%)	.06
Died within 90 days	62 (8.1%)	10 (1.2%)	$< .0001$

ICD-10 = International Statistical Classification of Diseases, 10th revision; SD = standard deviation.



**Figure** Patients according to D-dimer level on presentation, numbers admitted to hospital, numbers representing to the Danish health service within 90 days of presentation, and mortality within 90 days.

and unspecified soft tissue disorders. Many patients have several of these diagnoses simultaneously.

## Limitations

The diagnoses that were made in our study, both in the hospital and during 90-day follow-up, could not be scrutinized for accuracy. Therefore, we cannot be sure that venous thromboembolism and other diagnoses were not missed or overlooked in some patients, especially those with serious obvious disease such as metastatic cancer. Furthermore, we were not able to discern between active and inactive malignancy. Most of the patients in this single-center study were Caucasian. As D-dimer levels can vary in Afro-Caribbean and other racial groups,<sup>15,16</sup> our findings need to be confirmed in an ethnically diverse population. Age influences the level of D-dimer for the diagnosis of venous thromboembolic<sup>17</sup> disease and pulmonary embolus,<sup>18</sup> but it is not known if this is true for other diagnoses or the prediction of mortality. Based on previous work on mortality risk, we found that to retain a good sensitivity and likelihood ratio, no age-adjustment should be performed.<sup>19</sup> Although we chose a standard cut-off for D-dimer levels of 0.50 mg/L, it is possible that this might not have been optimal for all the variables we examined. In addition, we did not control for

factors that are known to be associated with elevated D-dimer levels, such as heparin use and pregnancy.<sup>8</sup>

## Interpretation

The practice of medicine requires the formulation of a diagnosis, prognosis, and treatment. We examined all the diagnostic codes recorded and do not know which, if any, was a “cause” of the patients presenting illness to the ED. Hypertension, for example, may just have been a commonly observed comorbidity. The immediate treatment of a diagnosis that is not associated with imminent death or severe morbidity may not be required, especially if the treatment is risky or expensive. On the other hand, if there is a slight possibility of a diagnosis that carries a high risk of imminent mortality or morbidity, treatment may be justified. This study confirms previous studies<sup>19,20</sup> that reported that D-dimer’s major clinical benefit is its ability to identify patients in whom imminent death is highly unlikely, even in those patients with conditions usually associated with mortality.

## Clinical Application

Results of this initial study of only 1600 patients suggest that D-dimer perhaps should be routinely measured for

**Table 2** Diagnoses Made Over 90 Days and at First Presentation (Grouped into Common ICD-10 Codes), and Their Associations with Elevated D-Dimer Levels\*

Diagnostic Groupings	ICD-10	Total	D-dimer ≥0.5 (%)	Odds Ratio	95% CI	Chi-squared	P Value
<b>Made over 90 days</b>							
Infection	See Ref 12	487	68.4%	3.47	2.74 4.39	121.29	<.0001
HTN	I10-16	184	45.7%	0.92	0.67 1.27	0.20	.66
COPD	J40-47	138	48.6%	1.05	0.73 1.51	0.03	.86
Cancer	See <a href="#">Supplementary Table</a> (available online)	147	72.8%	3.28	2.21 4.89	40.52	<.0001
CVA	I60-69	60	43.3%	0.84	0.48 1.46	0.27	.60
TIA	G45	32	43.8%	0.86	0.40 1.84	0.06	.81
VTE	See <a href="#">Supplementary Table</a> (available online)	72	83.3%	5.92	3.04 11.77	37.41	<.0001
Heart failure	I50	74	66.2%	2.25	1.34 3.81	10.17	.001
Unspecified dyspnea	R06	67	40.3%	0.74	0.43 1.25	1.15	.28
Acute myocardial infarction	I21	42	45.2%	0.91	0.47 1.77	0.02	.89
Anemia	D50-53,63-64	42	66.7%	2.26	1.13 4.58	5.62	.02
Unspecified soft tissue disorders	M79	27	70.4%	2.67	1.09 6.73	4.89	.03
Functional GI disorders	K59	14	71.4%	2.79	0.80 10.70	2.36	.12
None of the above	-	718	32.0%	0.32	0.26 0.39	122.39	<.0001
<b>Made at first presentation</b>							
Infection	See Ref 12	394	69.8%	3.43	2.67 4.43	103.19	<.0001
HTN	I10-16	139	41.0%	0.75	0.52 1.09	2.26	.13
COPD	J40-47	108	48.1%	1.03	0.68 1.56	0.00	.96
Cancer	See <a href="#">Supplementary Table</a> (available online)	82	75.6%	3.65	2.12 6.34	26.29	<.0001
CVA	I60-69	50	42.0%	0.80	0.43 1.46	0.41	.52
TIA	G45	25	40.0%	0.73	0.30 1.76	0.30	.58
VTE	See <a href="#">Supplementary Table</a> (available online)	54	90.7%	11.53	4.34 33.31	40.20	<.0001
Heart failure	I50	55	60.0%	1.69	0.94 3.05	3.09	.08
Unspecified dyspnea	R06	47	36.2%	0.62	0.32 1.18	2.03	.15
Acute myocardial infarction	I21	30	40.0%	0.73	0.33 1.63	0.41	.52
Anemia	D50-53,63-64	33	75.8%	3.54	1.50 8.65	9.69	.002
Unspecified soft tissue disorders	M79	20	60.0%	1.67	0.63 4.53	0.82	.37
Functional GI disorders	K59	8	75.0%	3.34	0.60 24.29	1.46	.23
None of the above	-	765	40.0%	0.37	0.30 0.45	96.11	<.0001

CI = confidence interval, COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; GI = gastrointestinal; HTN = hypertension; ICD-10 = International Statistical Classification of Diseases, 10th revision; TIA = transient ischemic attack; VTE = venous thromboembolism.  
 \*All statistically significant associations in italics.

**Table 3** Number of Patients Simultaneously Coded with Diagnostic Groupings Associated with Elevated D-Dimer Levels\*

Diagnostic Grouping	Infection	Cancer	Heart Failure	VTE	Anemia	Soft Tissue Disorder
Infection	345	72	27	20	19	4
Cancer	72	50	7	8	9	1
Heart failure	27	7	34	1	4	1
VTE	20	8	1	38	4	1
Anemia	19	9	4	4	6	0
Soft tissue disorder	4	1	1	1	0	20
Total	487	147	74	72	42	27

VTE = venous thromboembolism.  
 \*Diagnoses were made from time of presentation to up to 90 days afterward.

**Table 4** Association Between All Diagnostic Groupings Associated and 90-day Mortality

Diagnostic Grouping	Odds Ratio	95% CI		Chi-squared	P Value
<b>All patients</b>					
Cancer	12.06	7.06	20.59	136.89	<.0001
Infection	4.41	2.61	7.47	38.89	<.0001
VTE	1.27	0.38	3.80	0.03	.87
Heart failure	4.77	2.29	9.76	22.29	<.0001
Anemia	3.80	1.37	9.93	7.52	.006
Soft tissue disorders	0.00	0.00	3.99	0.44	.51
<b>D-dimer ≥0.5 mg/L</b>					
Cancer	7.62	4.21	13.79	63.29	<.0001
Infection	2.19	1.24	3.88	7.89	.005
VTE	0.80	0.23	2.42	0.03	.86
Heart failure	4.32	1.98	9.31	16.59	<.0001
Anemia	3.32	1.14	9.17	5.20	.02
Soft tissue disorders	0.00	0.00	3.04	0.78	.38
<b>D-dimer &lt;0.5 mg/L</b>					
Cancer	22.91	5.37	97.99	36.49	<.0001
Infection	18.93	3.64	132.15	21.96	<.0001
VTE	0.00	0.00	41.73	0.93	.33
Heart failure	0.00	0.00	18.52	0.15	.70
Anemia	0.00	0.00	35.09	0.70	.40
Soft tissue disorders	0.00	0.00	66.41	1.78	.18

CI = confidence interval; VTE = venous thromboembolism.

**Table 5** 90-Day Mortality of Patients According to Diagnostic Grouping and D-Dimer Level\*

Diagnosis	n	D-Dimer Level			
		≥0.5 mg/L		<0.5 mg/L	
		Number of Patients (%)	90-day Mortality	Number of Patients (%)	90-day Mortality
Cancer	147	107 (73%)	28.0%	40 (27%)	12.5%
Unspecified breathing abnormality	67	27 (40%)	18.5%	40 (60%)	10.0%
COPD	138	67 (49%)	10.4%	71 (51%)	7.0%
Infection	487	333 (68%)	9.9%	154 (32%)	5.2%
Hypertension	184	84 (46%)	7.1%	100 (54%)	0.0%
Heart failure	74	49 (66%)	24.5%	25 (44%)	0.0%
VTE	72	60 (83%)	6.7%	12 (17%)	0.0%
Stroke	60	26 (43%)	15.4%	34 (57%)	0.0%
Anemia	42	28 (67%)	21.4%	14 (33%)	0.0%
Acute myocardial infarction	42	19 (45%)	15.8%	23 (55%)	0.0%
TIA	32	14 (44%)	0.0%	18 (56%)	0.0%
Unspecified soft tissue disorder	27	19 (70%)	0.0%	8 (30%)	0.0%
Functional GI disorder	14	10 (71%)	40.0%	4 (29%)	0.0%
None of the above	718	230 (32%)	2.6%	488 (68%)	0.0%

COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; VTE = venous thromboembolism; TIA = transient ischemic attack.

\*Sorted by mortality of patients with normal D-dimer levels.

every patient presenting with an acute medical illness. The current coronavirus pandemic vindicates this suggestion, as COVID-19 patients with mild disease all had persistently normal D-dimer levels.<sup>21</sup> The objection to measuring D-dimer on every ED patient is that it would result in an increase in unnecessary investigations. D-dimer is a useful test to rule out venous thromboembolic disease in patients at low to intermediate risk, but a positive test must be interpreted with great caution as it could indicate venous thromboembolism but could also reflect the presence of a host of other conditions, either alone or in conjunction with venous

thromboembolism. Because patients with an elevated D-dimer are at greater risk, they urgently require clinical acumen and skill to address every possibility,<sup>19</sup> whereas a normal D-dimer level should allow the luxury of more time to make a diagnosis and consider appropriate treatment.

**CONCLUSION**

In our study, nearly half of all the ED patients had an elevated D-dimer level, and these patients were more likely to be admitted to hospital and to re-present within 90 days.

They were also 7 times more likely to die during this time. Elevated D-dimer levels are not only associated with an increased risk for VTE, but are also associated with infection, cancer, heart failure and anemia.

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## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjmed.2020.06.009>.



**Supplementary Table** Cancer and Venous Thromboembolism Codes

Cancer Codes	Venous Thromboembolism Codes
C139	I236B
C159M	I260
C160	I269
C169	I269A
C178M	I800
C179	I800B
C180	I802
C182	I802B
C183	I803
C183M	I803B
C184	I803C
C184M	I803E
C185	I803F
C187	I808
C189	I808A
C189M	I808B
C209	I809
C209M	I819
C220	I829
C220M	I829B
C221A	Z921
C229	
C240	
C241	
C249	
C250	
C250M	
C259	
C259M	
C340A	
C341	
C343	
C343M	
C349	
C349M	
C349X	
C412A	
C430	
C438	
C439	
C439M	
C442	
C443	
C445	
C447	
C449	
C499	
C509	
C509M	
C519	
C519M	
C539	
C539M	

**Supplementary Table** (Continued)

Cancer Codes	Venous Thromboembolism Codes
C539X	
C549	
C569	
C579	
C609	
C619	
C619M	
C649	
C649M	
C649X	
C679	
C699	
C709X	
C711	
C712	
C713	
C714	
C718	
C719	
C739	
C749	
C770G	
C771	
C771B	
C773	
C779	
C779A	
C780	
C781	
C782	
C786	
C786A	
C787	
C790B	
C791I	
C793	
C793A	
C795	
C795B	
C795E	
C797	
C798	
C800M	
C809	
C809M	
C810	
C829	
C830	
C831	
C833	
C865	
C880	
C900	
C910	

**Supplementary Table** (Continued)

Cancer Codes	Venous Thromboembolism Codes
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C911	
C914	
C920	
C920D	
C920F	
C921	
C923	
C929	
C931	
D032A	
D049	
D095	
D462A	
D462B	
D469	
D630	
E340	
Z031	
Z031A	
Z031B	
Z031BR	
Z031C	
Z031D	
Z031DA	
Z031DB	
Z031E	
Z031F	
Z031H	
Z031H1	
Z031J	
Z031K1	
Z031K2	
Z031K3R	
Z031R	
Z031S	
Z031T	
Z031W	
Z031X	
Z031XAR	
Z031Y	
Z031YB	
Z031Z	
Z038E	
Z850D	
Z851	
Z853	
Z855	
Z858	
Z859	
Z926	