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COVID-19 infection: The risk of a coagulation disorder is lower in children than in adults

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Abstract

The severity of COVID-19 infection increases with age being least in children (but not zero) and greater as one ages in adult life with the most advanced disease and highest mortality rate occurring in those greater than 65 years of age. One of the critical factors associated with advanced disease and mortality regardless of age is the existence of a hypercoagulopathy/diffuse intravascular thrombotic state, particularly involving the microcirculation. In an effort to identify coagulation markers that differ between those present at hospital admission in a young population (child and young adult less than 19 years of age) and adults greater than 65 years of age that might identify a difference in coagulant abnormalities the following study was initiated. The clinical profiles of the young adults aged less than 19 years and the older adult population greater than 65 years of age did not differ in terms of signs and symptoms with the exception new onset dyspnea present in the older age group. However, the measures of coagulation factors assessed in the study differed significantly between the two groups being abnormal in the older adults as compared to the children and young adults ($p < 0.05$). Interestingly, the single clinical complaint that differed between the groups was the presence of new onset dyspnea in the oldest group. This suggests that the combination of new onset dyspnea and abnormal coagulation test results may be the initial clinical finding that identifies individuals that are likely to progress to a clinically evident hypercoagulant state as a consequence of their COVID-19 infection. If such could be identified, the subset of individuals manifesting an early subclinical hypercoagulant state might benefit from anticoagulant therapy that inhibits the development of an overt hypercoagulant state that progresses to the hypercoagulant-intravascular microthrombotic disorder associated with death in the COVID-19 infected elderly population.

Introduction

Since the earliest recognition of COVID-19 disease and its subsequent designation as a pandemic (1), it has been observed that COVID-19 infection in terms of clinical signs and symptoms is less severe in children and young adults as compared to older adults (2). Moreover, there is an increasing prevalence of severe disease and death in the older age group. Thus, in the United States 31% of cases occurring in adults greater than 85 years of age account for 53% of advanced cases and experience a death rate of 80% (2,3). The cause of death in addition to hypoxia as a result of their progressive pulmonary disease is the presence of a critical inflammatory response with the development of a hypercoagulable state, that progresses to a disseminated intravascular microthrombotic disease process (2-4). The present study was designed to determine what coagulation abnormalities might occur in COVID 19 infected individuals at the time of hospitalization that could identify those that might benefit from anticoagulant therapy to prevent the progression to a diffuse intervascular hyperthrombotic disease state (2-4).

Methods

The study populations consisted of 62 patients randomly selected from the 289 admitted to the Infectious and Tropical Disease Hospital mandated by the municipal government to be responsible for the health care of infected COVID-19 individuals between March 3, 2020 through March 28, 2020. Thirty four individuals less than 19 years of age ranging from 1 to 19 years (Group 1) and twenty-eight greater than sixty-four years of age were identified(Group 2) and enrolled in the present investigation. All were positive for COVID-19 by reverse transcriptase PCR, the single requirement for hospitalization.

The coagulation markers utilized for this investigated consisted of routine coagulation tests required of all patients admitted to the hospital consisting of a platelet count, prothrombin time, INR,

quick time and prothrombin index (5,6). As these tests are readily available in all hospitals and clinics in Romania. In addition, one of the goals was to identify individuals with increased evidence of a hypercoaguable state such that they might be treated with anticoagulants at an early time to prevent progression to a diffuse hypercoaguable/microangiopathic state and an effort to reduce mortality.

Statistical Analysis

The data obtained from the medical records of these patients consisted of the identification of the signs and symptoms at admission that suggest COVID-19 infection as the specific indication for hospitalization. All 62 subjects were COVID-19 RNA positive. The basic coagulation measures identified at the time of admission were recorded. The data were analyzed to determine the prevalence of each parameter entered into the database in total and for each age group utilizing the Epi Info software obtained from the Center of Disease Control Atlanta, Georgia, USA (7). The difference between the data for each parameter between the two groups were analyzed using chi-square, Fischer's exact test for percents and ANOVA or Kruskal-Wallis (KW) H tests to identify the mean value for each group and identifying a significant difference between groups with a p value < 0.05.

Sampling

Sampling was not required as all of the cases in each subgroup were consecutively hospitalized between March 3 and March 28.

Ethical Approval

The personal data of the subjects (age, gender, occupation) were imported from the individual case investigation forms, the legal document, required for continued public health hospitalization and was exempted from board evaluation and approval.

Results

The prevalence of clinical complaints between the two groups in terms of fever, diarrhea, fatigue, or myalgia were similar $p>0.05$ except for the complaint of new onset dyspnea(Table 1). The prevalence of an abnormal anticoagulation biomarker was statistically significant between the senior age group and the junior age group $p <0.05$ (Table 1).

A significant difference in the prevalence of abnormal coagulation tests at admission was identified in the senior group (36.6%) as compared to 2.9% in the junior age group. Each abnormal coagulation test result in the senior age group as compared to the same result present in the younger age group (relative risk 1.76: 97% CI) (1.58-7.13); p 0.0014)was identified for each parameter assessed (Table 2)

Discussion

Despite no difference between the clinical symptoms reported at the time of hospital admission was identified except for new onset dyspnea in the older age group. The prevalence of abnormal coagulation tests was highly significantly different between the two age groups (Table 2). The recognition of coagulation abnormalities associated with severe acute respiratory syndrome in individuals with a SARS infection that can progress to a disseminated intravascular coagulopathy (DIC) has been identified previously (8-10). This finding was confirmed in the present study of the individuals with COVID-19. Mild clinical abnormalities being associated with minimal coagulation dysfunction that progresses in the elderly population, particularly those greater than 65 years of age (15-19). Several previous publications have identified an association between older age and the morbidity and mortality due to COVID-19 (11-14). The present findings are consistent with reports of minimal coagulation abnormalities occurring in children as compared to adults particularly older adults with a COVID-19 infection (16-19). The present study confirms these early results (16-19) but extends them by suggesting that their absence pretends a milder less severe disease and greater likelihood of survival at the time of hospital admission for the younger age group. The presence of identifiable abnormal coagulation results at admission in older adults at the time of initial hospitalization suggests that the onset of the coagulant abnormalities occurring in the elderly, has its onset early in the course of the COVID-19 infection. It also suggests that initiation of anticoagulant therapy once any evidence of a progressive coagulopathy is observed, regardless of individual's age, but particularly in the elderly should be initiated

Table 1: Distribution of clinical manifestations of COVID-19 infection at the time of hospitalization

Symptoms at hospital admission	Prevalence by shown groups		Relative Risk (95% Confidence Interval)	*p* value
	Senior (N=28)	Junior (N=34)		
Asymptomatic	7.4 %	17.6 %	0.41 (0.09 – 1.91)	0.2157
Fever (≥ 38° C)	19.2 %	26.5 %	0.72 (0.27 – 1.91)	0.3665
Diarrhea	3.8 %	5.9 %	0.65 (0.06 – 6.82)	0.6011
Fatigue	11.5 %	2.9 %	3.92 (0.43 – 35.57)	0.2119
Myalgia	11.1 %	8.8 %	1.25 (0.27 – 5.74)	0.5473
Dyspnea	34.6 %	2.9 %	1.76 (1.58 – 7.13)	0.0014*

Table 2: Distribution by age of coagulation abnormalities in younger and older adults infected with COVID-19 at admission

Coagulation biomarker (symbol)	Prevalence in subjects with abnormal values by groups (6)		Relative Risk (95 % Confidence Interval)	*p* value
	Senior (N=28)	Junior (N=34)		
Platelet number	53.6 %	5.9 %	9.10 (2.27 – 36.49)	0.0000
Prothrombin Index	32.0 %	3.8 %	8.32 (1.12 – 61.79)	0.0099
INR	32.0 %	3.8 %	8.32 (1.12 – 61.78)	0.0099
Quick time	44.00 %	11.5 %	3.81 (1.20 – 12.07)	0.0103

to reduce the risk of its progression to a microvascular thrombotic disease and death.

Limitations of the study

The major limitations of this study are that the patient sample size was small and by the limited number of coagulant tests utilized. A larger number of measures utilized that reflect the presence of a dysfunctional coagulation system, most obviously being the D-dimer test, would have added value to the findings. Unfortunately, this test is only selectively utilized in the hospital wherein the present investigation was accomplished.

Conclusion

The present study identified the fact that elderly patients with mild to minimal coagulation abnormalities having COVID-19 infection are highly likely to progress to a hyperthrombotic disease process resulting in a reduced survival rate as a result of the presence of a hyperthrombotic, microthrombotic disease process in older individuals with a COVID-19 infection. This process can culminate in an overt DIC/hypercoaguable state with diffuse microvascular thrombosis resulting in a death rate exceeding 80%. Further, it suggests that early anticoagulant therapy may halt the progression of this process resulting in lives saved.

Conflict of interest

None declared by the investigators.

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