Haematological parameters in severe acute respiratory syndrome

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Summary Clinical presentation of severe acute respiratory syndrome (SARS) is non-specific and isolation of all suspected patients is difficult because of the limited availability of isolation facilities. We studied changes in haematological parameters in SARS patients using median values analysed according to the day of symptom onset. White cell (WCC), absolute neutrophil, absolute lymphocyte (ALC) and platelet counts followed a v-shaped trend with the nadir at day 6 or 7 after symptom onset except for ALC in the ICU group that had not reached the nadir by day 12. None of our patients had a platelet count $< 80 \times 10^9$/l and WCC $< 2 \times 10^9$/l in the first 5 days of symptoms and these parameters may allow early stratification of febrile patients into likely and unlikely SARS cases to allow effective utilization of isolation facilities. On multivariate analysis, age is the only independent predictor for ICU admission.

Keywords Severe acute respiratory syndrome, prognosis, haematological parameters

Introduction

A global alert for the severe acute respiratory syndrome (SARS) was issued by the World Health Organization (WHO) in March 2001 (WHO, 2003). One of the largest outbreaks occurred in Singapore with most of the patients managed in a single SARS-designated hospital. Mortality in patients requiring Intensive Care Unit (ICU) management was very high (Lew *et al.*, 2003). The cause of SARS has been identified as a novel coronavirus (Drosten *et al.*, 2003; Ksiazek *et al.*, 2003; Peiris *et al.*, 2003a).

The WHO clinical case definition of SARS is highly insensitive highlighting the non-specific nature of presenting symptoms (Rainer *et al.*, 2003). Although sequencing of the coronavirus genome (Marra *et al.*, 2003; Rota *et al.*, 2003) has allowed the development of more specific diagnostic tests, none of these are fully validated and widely available. During the SARS outbreak, tremendous burden was placed on hospitals to provide isolation facilities because of the highly infectious nature of the

coronavirus. It would be helpful if some routine laboratory tests could help to stratify patients with compatible clinical features early to allow for efficient use of limited isolation facilities. Furthermore, early identification of patients with a poor prognosis may allow early intervention to improve outcome.

In a large cohort of confirmed SARS cases, we retrospectively analysed their haematological parameters with the aims of describing changes in these parameters as the infection progressed, identifying early haematological markers helpful in excluding SARS and predicting patients needing ICU admission.

Patients and methods

Patients

A retrospective review of SARS cases confirmed by serological testing or identification of viral RNA by reverse-transcriptase polymerase chain reaction (RT-PCT) from 15 March to 12 May 2003 was conducted. The following patients were excluded from the final analysis: patients not treated at the SARS-designated hospital; patient <9 years old and patients whose history of symptom onset is unclear. The study was approved by the hospital's ethics review board.

Data collected

The patients were divided into two groups, those admitted to ICU and those not. Sequential results of haematological indices including haemoglobin (Hb), white cell (WCC), platelet, absolute neutrophil (ANC) and absolute lymphocyte counts (ALC) were obtained for each patient and tabulated according to day of illness. The day of symptom onset is designated day 1 of illness. Other data collected include demographics, co-morbid conditions (chronic airways disease, cardiovascular disease, diabetes mellitus, acute or chronic renal failure), and days from symptom onset to hospital admission and ICU admission.

Statistics

The median and range were calculated for each haematological parameter. For predictors of ICU admission, the maximum or minimum value (whichever appropriate) from days 2 to 5 was used, and potential predictors were identified using univariate and multivariate logistic regression analysis. Data analysis was carried out in Stata (V7.0; StataCorp LP, College Station, TX, USA), and level of significance was set at 5%.

Results

Patient cohort

A total of 185 confirmed SARS cases met our inclusion criteria during the study period. Of these, 145 did not require ICU management. The characteristics of the two groups are presented in Table 1.

Haematological characteristics of patients with SARS

Proportion of patients with abnormal haematological indices at different stages of infection is presented in Table 2.

Table 1. Characteristics of SARS patients in ICU and non-ICU groups

	Non-ICU group	ICU group	Overall
Number	145	40	185
Median age, years (range)	34 (9–74)	50 (19–78)	36 (9–78)
Male : female ratio	1 : 2.37	1 : 1.05	1 : 1.98
Median time (days) from onset of symptoms to hospital admission (range)	4 (1–12)	5 (1–11)	4 (1–12)
Median time (days) from onset of symptoms to ICU admission (range)	NA	11 (5–16)	11 (5–16)
Co-morbidity	14 (9.7%)	15 (37.5%)	29 (15.7%)
Mortality (%)	0/145 (0%)	18/40 (45%)	18/185 (9.7%)

Table 2. Percentage of patients in non-ICU and ICU groups with abnormal haematological indices

Indices	By day 5 of symptoms			By day 10 of symptoms		
	Non-ICU ($n = 103$)	ICU ($n = 19$)	Overall ($n = 122$)	Non-ICU ($n = 143$)	ICU ($n = 37$)	Overall ($n = 180$)
WCC $< 2 \times 10^9$/l	0 (0%)	0 (0%)	0 (0%)	3 (2.1%)	3 (8.1%)	6 (3.3%)
WCC $< 4 \times 10^9$/l	21 (20.4%)	3 (15.8%)	24 (19.7%)	78 (54.5%)	12 (32.4%)	90 (50%)
WCC $> 10 \times 10^9$/l	3 (2.9%)	3 (15.8%)	6 (4.9%)	7 (4.9%)	7 (18.9%)	14 (7.8%)
Polymorphs $< 1 \times 10^9$/l	2 (1.9%)	0 (0%)	2 (1.6%)	7 (4.9%)	2 (5.4%)	9 (5%)
Polymorphs $< 2 \times 10^9$/l	15 (14.6%)	1 (5.2%)	16 (13.1%)	50 (34.9%)	4 (10.8%)	54 (30%
Polymorphs $> 4 \times 10^9$/l	49 (37.6%)	15 (78.9%)	64 (52.5%)	82 (57.3%)	28 (75.7%)	110 (61.1%)
Lymphocytes $< 0.5 \times 10^9$/l	9 (8.7%)	3 (15.8%)	12 (9.8%)	23 (16.1%)	11 (29.7%)	34 (18.9%)
Lymphocytes $< 1 \times 10^9$/l	60 (58.2%)	15 (78.9%)	75 (61.5%)	111 (77.6%)	34 (91.9%)	145 (80.6%)
Lymphocytes $> 2 \times 10^9$/l	2 (1.9%)	1 (5.3%)	3 (2.5%)	9 (6.3%)	1 (2.7%)	10 (5.6%)
Platelet $< 80 \times 10^9$/l	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (2.7%)	2 (1.1%)
Platelet $< 100 \times 10^9$/l	3 (2.9%)	0 (0%)	3 (2.5%)	7 (4.9%)	3 (8.1%)	10 (5.6%)
Platelet $> 150 \times 10^9$/l	86 (83.5%)	14 (73.7%)	90 (73.8%)	128 (89.5%)	31 (83.4%)	159 (88.3%)

Values are as number of patients (%).

Although leucopenia (WCC $< 4 \times 10^9$/l) occurred in 19.7 and 50% of patients with available blood tests by days 5 and 10 of symptom onset respectively, severe neutropenia (ANC $< 1 \times 10^9$/l) was rare (1.6 and 5% of patients by days 5 and 10 respectively). A WCC $< 2 \times 10^9$/l was also rare, affecting only 3.3% of patients and only occurring after day 5 of illness. Most patients (61.5% by day 5 and 80.6% by day 10) developed moderate lymphopenia (ALC $< 1 \times 10^9$/l) at some point during the first 10 days of illness. However, severe lymphopenia (ALC $< 0.5 \times 10^9$/l) was rare occurring in only 9.8 and 18.9% of patients by days 5 and 10 of symptoms respectively. Reactive lymphocytes commonly seen in viral infections were also conspicuously absent in patients with SARS.

The majority of patients had a normal platelet count ($>150 \times 10^9$/l). 88.3% of patients never had a platelet count $< 150 \times 10^9$/l. In fact, none of the 122 patients who were tested during the first 5 days of illness had a platelet count $< 80 \times 10^9$/l. By day 10 of illness, only two of 180 patients (1.1%) tested had a platelet count $< 80 \times 10^9$/l.

Changes to haematological indices during infection

By plotting the median values for each haematological parameter over a period of 12 days from symptom onset, time trends for changes to Hb, WCC, platelet count, ANC and ALC were obtained (Figure 1).

The Hb for both groups continued to fall during the first 12 days of illness (graph not shown). The WCC initially decreased, reaching a nadir at day 7 or 8 of illness. The median nadir WCC was 4×10^9/l (range $2–12 \times 10^9$/l for non-ICU and $2–14.5 \times 10^9$/l for ICU group) for both groups. Changes in the ANC reflected changes in the WCC. The median nadir ANC was 2.66×10^9/l (range $1.08–8.85 \times 10^9$/l) for the non-ICU group and higher for the ICU group at 2.8×10^9/l (range $1.29–12.7 \times 10^9$/l).

A striking feature of the ALC graphs was the lack of lymphocyte recovery in the ICU group. For non-ICU patients, the ALC reached a nadir at day 8 of illness at a median level of 0.79×10^9/l (range $0.27–1.91 \times 10^9$/l) but the nadir had not been reached by day 12 of symptoms for the ICU group.

The platelet trend followed that of WCC and ANC. The platelet count reached a nadir at day 6 of illness for the non-ICU group and day 7 of illness for the ICU group with median nadir platelet count of 161×10^9/l (range $81–377 \times 10^9$/l) and 151×10^9/l (range $61–314 \times 10^9$/l) respectively.
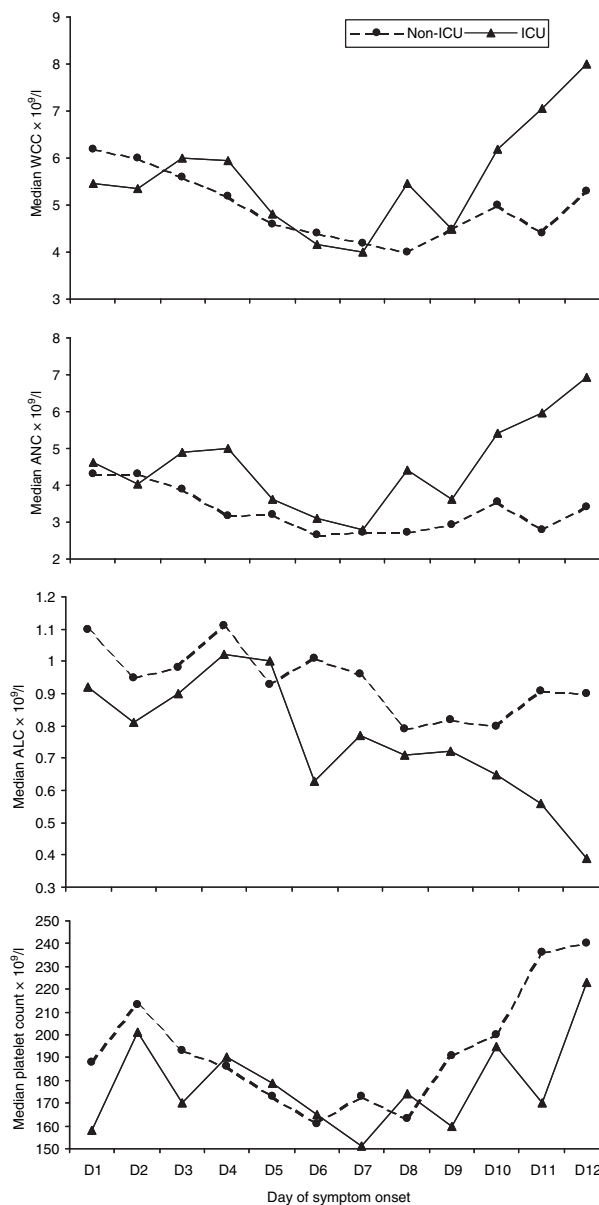
Figure 1. Time trend of haematological parameters in ICU and non-ICU groups.

Identification of prognostic markers

In the univariate analysis, sex, age, presence of co-morbid conditions, WCC and ANC were found to be significant predictors of ICU admission (Table 3). However, in the multivariate analysis, only age was significant.

Discussion

SARS is an emerging infectious disease with many aspects of its pathophysiology and clinical behaviour still not fully understood. This has hampered progress in its

Covariates	OR	95% CI	*P*-value
Sex (male)	2.15	(1.05–4.39)	0.036
Age (10 year increase)	1.68	(1.32–2.14)	<0.001
Presence of co-morbid conditions	3.29	(1.37–7.89)	0.008
Hb in g/dl (1 g/dl increase)	1.06	(0.77–1.45)	0.720
WCC in 10^9/l (1×10^9/l increase)	1.20	(1.01–1.43)	0.034
ALC in 10^9/l (0.1×10^9/l increase)	0.91	(0.79–1.04)	0.171
Platelet count in 10^9/l (50×10^9/l increase)	1.00	(0.99–1.01)	0.506
Absolute neutrophil count (0.5×10^9/l increase)	1.11	(1.02–1.21)	0.021

Table 3. Demographic and haematological predictors of admission to ICU

Haematological values taken on days 2–5 of symptoms.

diagnosis and effective management. One of the main symptoms of SARS is fever. Fever is also common in other viral infections including dengue which is very common in Asia where the possibility of another SARS outbreak exists. Due to the highly infectious nature of the coronavirus, every febrile patient suspected of SARS screened at the screening centre need to be isolated. This led to a high demand for isolation beds, which is a limited resource in most acute care hospitals, during the SARS outbreak. Furthermore, the more specific serological test only becomes positive late in the course of the disease (Peiris *et al.*, 2003b), whilst RT-PCR for the coronavirus RNA have a detection rate of 79 and 80% in nasopharyngeal aspirate and plasma respectively during the first 3 days of illness (Grant *et al.*, 2003; Poon *et al.*, 2003). Any laboratory features in the first few days of fever that could suggest that the patient is unlikely to have SARS may obviate the need to isolate them in hospital.

We chose to study haematological indices as they are common laboratory investigations performed on patients admitted to hospitals with fever. Blood counts often provide useful clues regarding the diagnosis and complications of infectious disease. Some interesting observations were made.

In the first 5 days of illness, the majority of patients had a normal WCC with an elevated ANC and lymphopenia, and a normal Hb and platelet count. In this period, 61.5% of patients in our cohort had a moderate lymphopenia ($<1 \times 10^9$/l) although only 9.8% had ALC $< 0.5 \times 10^9$/l. This is comparable with other reported figures of 69.6 and 54% (Booth *et al.*, 2003; Lee *et al.*, 2003). The more recent Hong Kong study reported that 98% of their patients have moderate lymphopenia during the course of their illness (Wong *et al.*, 2003). This is comparable with our figure of 81% of patients having moderate lymphopenia by day 10 of illness. One of the notable features in SARS was that reactive lymphocytes were not commonly seen in the peripheral blood film. This contrasts with the common finding of reactive lymphocytes around the fourth and fifth day of fever in dengue which coincided with the recovery of the lymphocyte counts in these patients (Thisyakorn *et al.*, 1984).

The two Hong Kong studies reported thrombocytopenia ($<150 \times 10^9$/l) in 44.8% of patients on presentation and 55% of patients during the course of their illness respectively (Lee *et al.*, 2003; Wong *et al.*, 2003) but this was not a feature in our patients. Only 11.6% of our patients had a platelet count $< 150 \times 10^9$/l by day 10 of illness. In fact, within the first 5 days of illness, no patients had a platelet count $< 80 \times 10^9$/l or a WCC $< 2 \times 10^9$/l. By day 10, only two patients had a platelet count $< 80 \times 10^9$/l. One of these patients had pre-existing hepatocellular carcinoma with liver cirrhosis. The source of these differences between our study and the Hong Kong studies is uncertain and may be due to different variants of the coronavirus (Ruan *et al.*, 2003) exerting different effects on the patients or differences in treatment and study design. In contrast to our patients, the Hong Kong patients were routinely treated with prednisolone and ribavarin which may affect platelet and white cell count (Choi *et al.*, 2003). The analysis from Hong Kong included results from patients even after they were admitted to ICU. We only included blood results prior to ICU admission. This made our results more reflective of changes as a result of the coronavirus infection as they are not affected by the treatment given.

The absence of significant thrombocytopenia contrasted with patients with dengue who commonly has significant thrombocytopenia including severe thrombocytopenia ($<30 \times 10^9$/l) during the first week of illness (Nimmannitya, 1987). It would seem that patients presenting with severe thrombocytopenia ($<80 \times 10^9$/l) and a febrile illness are unlikely to have SARS. The same applies to patients presenting with a WCC $< 2 \times 10^9$/l. These parameters may therefore be helpful in stratification of febrile patients suspected of SARS into low and high-risk groups, and allow better allocation of the limited isolation rooms available.

Some early and late differences were observed in the various haematological parameters between the ICU and non-ICU groups. There is a clear difference in the median values of the Hb, WCC and ANC at day 3 and 4 of illness (Figure 1). The association of these parameters with ICU admission was tested in a logistic regression model incorporating other parameters like age and co-morbidities previously shown to have prognostic value (Booth *et al.*, 2003; Lee *et al.*, 2003).

In the univariate analysis, sex, age, presence of co-morbid conditions, WCC and ANC were found to be significant predictors. However, only age remained significant in the multivariate model. The recent Hong Kong study also failed to identify any haematological parameters predictive of ICU admission or death on multivariate analysis (Wong *et al.*, 2003). Our results contrasted with other studies that also identified elevated ANC (Lee *et al.*, 2003) and co-morbid conditions (Booth *et al.*, 2003) as independent predictors of poor outcome. However, these studies may not be directly comparable as we use the day of illness onset as our basis for data analysis rather than the day of presentation.

Late differences (from days 7 to 12 of symptom onset) included a greater increase in the WCC and the ANC following the nadir, and lack of recovery in the ALC by day 12 of illness in the ICU group. These differences may be a reflection of the greater severity of infection in the ICU group. Whether the persistent lymphopenia in the ICU group is as a result of the inability of these patients to mount an immune response resulting in more serious infection or because of bone marrow suppression caused by the virus is unknown.

This detailed study of haematological changes in one of the largest cohort of SARS patients managed in a single institution is strengthened by the use of the day of illness as the basis for data analysis compared with the day of presentation used by previous studies (Booth *et al.*, 2003; Lee *et al.*, 2003). This method removes the confounding effect caused by variation in the day of presentation. As laboratory measurements were not taken every day, one limitation of the study is the amount of missing data that could bias our results.

In conclusion, most haematological indices follow a v-shaped pattern in SARS. An exception is the ICU group who had not recovered their ALC by day 12 of symptoms. A platelet count $< 80 \times 10^9/l$ and a WCC $< 2 \times 10^9/l$ were not encountered in any SARS patient in the first 5 days of illness. Moderate lymphopenia is common but ALC $< 0.5 \times 10^9/l$ was uncommon in the early phase of the illness. The absence of reactive lymphocytes is another important feature distinguishing SARS from other viral infections. These features may be helpful in the early stratification of patients with clinical features compatible with SARS into a low risk group possibly obviating the need for isolation.

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