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Short Communication

Soluble interleukin-2 receptor levels on admission associated with mortality in coronavirus disease 2019

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\textbf{A B S T R A C T}

**Objectives:** Early and simple detection of high-risk groups is crucial for minimizing severe coronavirus disease 2019 (COVID-19)-related deaths. Soluble interleukin 2 receptors (sIL2R) have been suspected as being prognostic markers for infectious diseases. This study validated the usefulness of sIL2R as a marker for deaths related to COVID-19.

**Methods:** This retrospective observational study enrolled participants who showed positive results for severe acute respiratory syndrome coronavirus 2 RNA admittance to the hospital between 01 April and 30 September 2020. Of the 102 patients enrolled in this study, sIL2R levels were measured in 87 patients. For comparisons between survival and non-survival groups, potential confounding variables were entered into univariate models, and variables showing significant correlations ($p < 0.05$) in those models were added to a multivariate model.

**Results:** Being aged $> 60$ years and sIL2R levels $> 1060$ U/ml were significantly associated with mortality on univariate analyses; only sIL2R levels significantly correlated with mortality on multivariate logistic regression analysis. Further, sequential sIL2R levels in three patients were increased at progression or death.

**Conclusion:** sIL2R on admission and sequential monitoring of sIL2R might reflect disease severity.

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In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections developed in Wuhan, China, and subsequently spread throughout the world. Several risk factors or predictors of disease severity have been reported, and severe coronavirus disease 2019 (COVID-19) has been correlated with various immunological abnormalities, cytokine release, and coagulation cascade. An important step towards avoiding increasing numbers of COVID-19-related deaths is early and simple detection of high-risk groups.

This retrospective observational study was performed at Toyama Prefectural Central Hospital in Japan. All patients who tested positive for SARS-CoV-2 RNA and admitted to the hospital between 01 April and 30 September 2020 were enrolled. The primary outcome measure was infectious death. To estimate potential clinical relevance, the following were collected: baseline, clinical and laboratory data, and outcomes as parameters: age, sex, and measured values of soluble interleukin 2 receptor (sIL2R), CD4/CD8 double positive cell, procalcitonin (PCT), and thrombin-antithrombin complex (TAT). Previous reports have suggested sIL2R as a marker for activated lymphocytes (Murakami et al., 2019). Immunologic criteria for provisional diagnosis of hemophagocytic lymphohistiocytosis include elevated levels of sIL2R (Filipovich, 2009). The test for sIL2R is also easier and faster than for other cytokines. This study tested levels of sIL2R.

On univariate analyses, the $\chi^2$ or Fisher’s exact test was used for categorical variables. Cox-regression analysis was applied to identify predictors of death on multivariate analysis. Cut-off values were determined by receiver operating characteristic (ROC) curve analysis and patients were allocated into two groups on the basis of these cut-off values. In addition, relationships between groups determined using those cut-offs for each factor and outcomes were analyzed. EZR version 1.54 was used for all statistical analyses (Kanda, 2013).

A total of 102 patients were enrolled in this study. Of these, 42 patients had data available for the CD4/25 double-positive cell count. Levels of sIL2R were measured in 87 patients, PCT levels in 93 patients, and TAT levels in 40 patients. Four patients underwent sequential measurement of sIL2R levels at diagnosis, progression, and recovery or death. Cut-off values were determined by ROC.
curve analysis. Cut-off values for CD4/25 cell count, sIL2R, PCT, and TAT to predict outcomes were 90/μl, 1060 U/ml, 0.15 ng/ml, and 4 ng/ml, respectively. Table 1 shows mortality rates for groups by risk factor. Being aged ≥60 years and sIL2R levels ≥1060 U/ml significantly correlated with mortality on univariate analyses. Only sIL2R levels ≥1060 U/ml were significantly associated with mortality on multivariate logistic regression analysis based on the results of univariate analyses (Table 1). Multivariate analysis identified sIL2R as a significant independent risk factor. Two of sIL2R level ≥1060 U/ml seven patients had no pneumonia, another two patients of sIL2R level ≥1060 U/ml seven patients had pneumonia but no treatment of oxygen and other three patients of sIL2R level ≥1060 U/ml seven patients were severe condition but recovered. one of the two deaths with sIL2R <1060 U/ml is shown in Figure 1 as Case 1. Sequential sIL2R levels in Cases 1, 3 and 4 were increased at progression or death. On the other hand, the sIL2R level in Case 2 was decreased at recovery (Figure 1). The interval from diagnosis to progression was 2–4 weeks and that from progression to recovery or death was 2 weeks.

Zhou et al. reported older age and n-dimer level as potential risk factors that could help clinicians identify COVID-19 patients with poor prognosis at an early stage (Zhou et al., 2020). Other studies have identified PCT as a potential predictor of disease severity (Henry et al., 2020; Lippi and Plebani, 2020; Lippi et al., 2020). Severe COVID-19 patients show various immunological abnormalities, including reduced T-cell counts and cytokine release syndrome. Immune system hyperactivation and paralysis reportedly drive immunopathology in severe COVID-19 (Kalfagolu et al., 2020). Sugiyama et al. reported that serum CCL17 levels offer a predictive marker for distinguishing between mild/moderate and severe/critical disease in patients with COVID-19 (Sugiyama et al., 2020). From current data, only sIL2R levels ≥1060 U/ml significantly correlated with mortality on multivariate logistic regression analysis based on the results of univariate analyses. It was therefore considered that sIL2R offered a good reflection of COVID-19 severity. PCT may not have reflected the pathology of COVID-19 because of the complication of bacterial infection in the form of aspiration pneumonia among elderly patients. It was considered that the number of patients examined for TAT was too small to identify any significant correlation with outcome. Fewer CD4/25 double-positive cells tended to be associated with high mortality, contradicting the results for sIL2R; however, it was considered that the number of patients examined for CD4/25 was probably too small to show a significant correlation with outcome.

In summary, this study identified sIL2R as a predictive marker of cytokine release syndrome and immune overreaction against COVID-19. Since even patients with low sIL2R levels at diagnosis may progress to severe disease, and sIL2R might offer a predictor of disease severity, sequential monitoring of sIL2R may be warranted.

Conflict of interest

None declare.

Funding

None declare.

Ethical approval

Due to the observational and retrospective nature of the study, specific informed consent from individual patients was not required. All data were generated from routine standard clinical management of the patients.

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