TNF-related apoptosis-inducing ligand (TRAIL) protein as a marker for disease severity in patients with acute infection

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Abstract

BACKGROUND

TRAIL is a member of the tumor necrosis factor family implicated in programmed cell death. We recently demonstrated that TRAIL can serve as a useful biomarker for distinguishing between bacterial and viral infections when computationally combined with CRP and IP-10.[1-2] Here we report that low TRAIL concentration in the blood is significantly correlated with poor patient prognosis and higher disease severity.

METHODS

We studied 765 hospitalized and emergency department patients with acute infection and controls with no apparent infection, prospectively recruited between 2009 and 2013. Patient etiology (319 bacterial, 334 viral, and 112 non-infectious) was determined by a panel of three independent experts based on comprehensive clinical and laboratory assessment that included two multiplex-PCR panels applied to nasal swabs (Seeplex-RV15/PB6). Serum TRAIL levels were measured using commercially available ELISA kits (MeMed, IL).

RESULTS

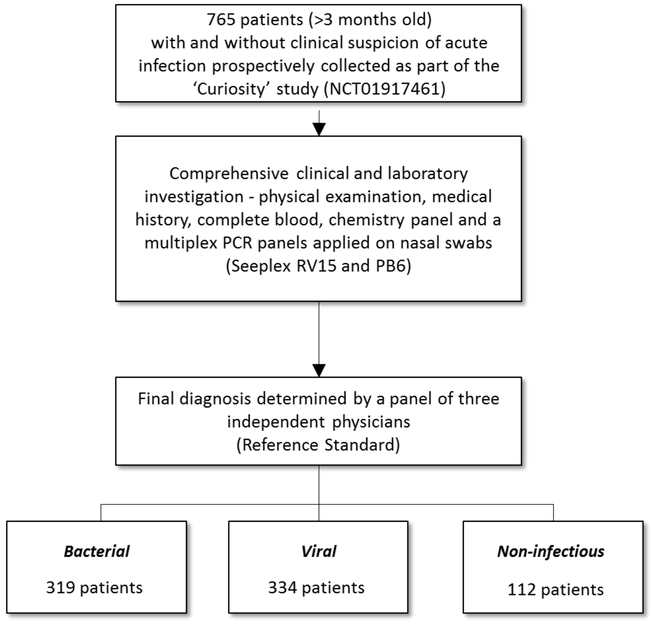
TRAIL serum levels were significantly decreased in bacterial patients and increased in viral patients as compared to controls (average±SD [pg/ml]: bacterial 45±33; viral 145±110; controls 77±32, $P<10^{-15}$). Further analysis of the infectious patients group (n=653), revealed that patients with TRAIL levels lower than 25 pg/ml (n=93), were characterized by more severe disease outcome compared to patients with higher TRAIL levels (n=560) including longer hospitalization duration (7.5±11.3 vs 1.9±2.2 days, $P<10^{-5}$), and need for mechanical ventilation and ICU admission (6/93 vs 0/560, $P<10^{-5}$). Severe clinical syndromes such as bacteremia and septic shock were also statistically enriched in the low TRAIL sub-group (64% (7/11) of all bacteremia cases $P<10^{-3}$, and 100% (7/7) of all septic shock cases, $P<10^{-6}$).

CONCLUSIONS

TRAIL serum levels lower than 25 pg/ml were correlated with longer hospitalization duration, ICU admission and severe clinical syndromes. These results suggest that TRAIL has the potential to serve as a marker for disease severity. Timely measurement of TRAIL serum levels might therefore enable a more accurate risk stratification, treatment optimization, and potentially better patient outcome.

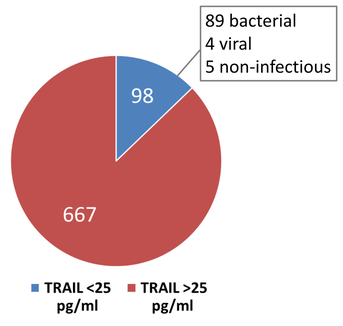
Methods

Study design



Monitoring prognostic measures in patients with low TRAIL levels

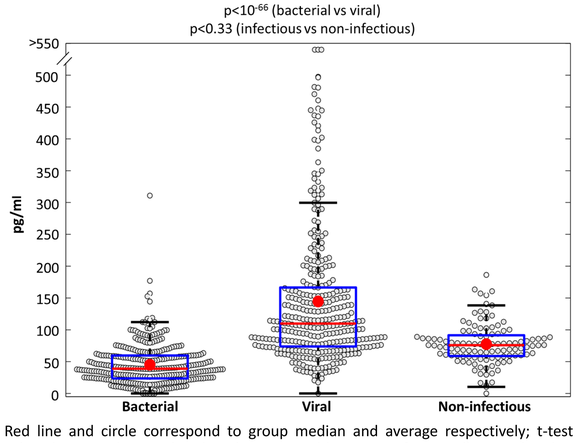
Patients were stratified according to their measured TRAIL levels (lower and higher than 25 pg/ml) and various clinical measures were used to retrospectively asses patient's disease severity such as ICU admission, need for mechanical ventilation or surgical interventions, hospital length of stay, and the manifestation of a severe clinical syndrome like bacteremia or septic shock.



Distribution of all study patients according to different serum TRAIL levels

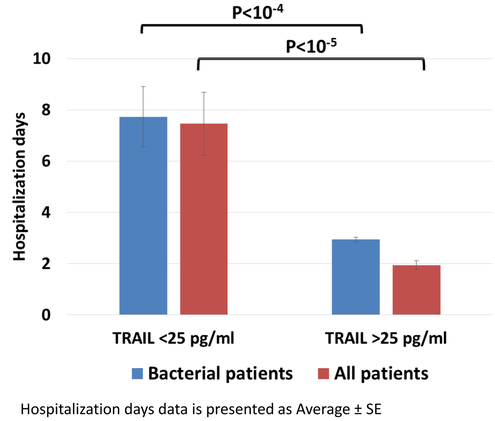
Results

1. TRAIL serum levels are decreased in bacterial patients and increased in viral patients



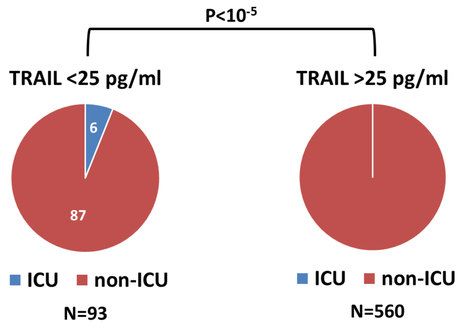
Red line and circle correspond to group median and average respectively; t-test p-values between bacterial and viral groups and between infectious (bacterial and viral) vs. non-infectious (including healthy subjects) are depicted.

2. Low TRAIL serum levels are associated with longer hospitalization duration

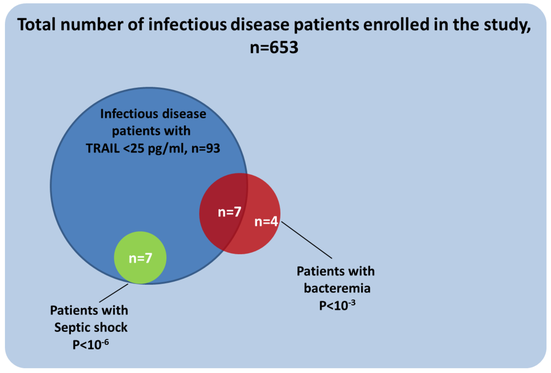


Hospitalization days data is presented as Average ± SE

3. Low TRAIL serum levels are associated with intensive care unit (ICU) admission



4. Patients with low TRAIL levels are statistically enriched in sub-group of patients with severe clinical syndromes



P-values were calculated using the hyper-geometric distribution

Discussion

Disease assessment is one of the most important tasks in management of infectious disease patients. As a complement to determining infection etiology, predicting patient prognosis may affect various aspects of patient management including treatment, diagnostic tests (e.g., microbiology, blood chemistry, radiology), and admission. Timely identification of patients with higher chance for poor prognosis may result in more aggressive patient management procedures including for example, ICU admission, advanced therapeutics, or invasive diagnostics, which could reduce complications and mortality. Here we report that low blood TRAIL levels are significantly correlated with poor patient prognosis and higher disease severity, and suggest TRAIL as a prognostic marker that has the potential to aid in correct patient stratification and management.

References

1. Oved et al. A novel host-proteome signature for distinguishing between acute bacterial and viral infections. *PLOS ONE* 2015
2. Eden et al. Diagnostic accuracy of a TRAIL, IP-10 and CRP combination for discriminating bacterial and viral etiologies at the ED. *J. Infect*. 2016.

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