Time-Varying Discrimination Accuracy of Longitudinal Biomarkers for the Prediction of Mortality Compared to Assessment at Fixed Time Point in Severe Burns Patients

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Abstract

Background: The distribution of biomarkers over time is considered an indicator of disease formation and helps in early detection of disease, thus reducing the disease-related mortality. The ability of biomarkers to predict outcomes has been evaluated using conventional cross-sectional methods; therefore, we investigated the prognostic potential of longitudinal biomarkers over time.

Methods: The patients aged > 18 y who were admitted within 24 h of the burn incident in the burn intensive care unit were enrolled. Longitudinal biomarkers, such as WBC, platelet count, lactate, creatinine, TB, and PT were retrieved from a clinical database warehouse. Time-dependent ROC curves using a cumulative/dynamic and incident/dynamic approach were employed to evaluate time-varying prognostic performance.

Results: Total 2259 patients were included in this retrospective study and divided into the survival group and non-survival group. With AUC using the ID approach, platelets showed the highest c-index with 0.930 (0.919 ~ 0.941) as well as the highest during all time points. PT and creatinine show over 8 c-index with 0.862 (0.843 ~ 0.881) and 0.828 (0.809 ~ 0.848), respectively.

Conclusions: The platelet count was the best prognostic marker. PT and creatinine also showed good overall diagnostic ability. Lactate is known as a strong predictor; however, it showed relatively poorer prognostic performance in burns.

Backgroud

Burns represent one of most devastating traumas and results in high morbidity and mortality. Thus, the prediction of adverse effects of interest or mortality using updated biomarkers that are measured routinely over time is an essential part of care in an intensive care unit (ICU). The distribution of biomarker over time is considered an indicator of disease formation and is helpful in the early detection of disease, thus reducing the disease-related mortality (1). Many biomarkers that are measured at a single time, such as at admission or an event, such as the development of acute kidney injury (AKI) or intervention, have been used to predict the outcome at multiple time points of interest.

If accurate predictions are possible, they could provide clinical recommendation about the selection and timing of interventions and help in the initiation of specific preventive strategies and aggressive treatment for high-risk individuals. Further, it could reduce the cost, adverse effects, and unnecessary interventions in low-risk patients. Ultimately, the goal of the prognostic model with the use of biomarkers is to accurately predict the time of the event or to distinguish cases and controls in every situation. In addition, the disease state of an individual changes over time; therefore, prognostic information, such as updated biomarkers recorded during routine measurements, also change and can affect the performance of decision-making tools.

The concept of accuracy of sensitivity and specificity is fundamental to clinical research and decision modeling. Recently, statistical methods have been developed to generalize these traditional cross-sectional accuracy concepts for the application to time-varying characteristics of disease states.(2) In clinical practice, the ability biomarkers to predict the outcome have been evaluated using a conventional, cross-sectional method. Therefore, we investigated the prognostic potential of biomarkers routinely used in clinical practice over time and compared whether different biomarkers have varying prognostic accuracy at different times during treatment.

Methods

From February 2007 to December 2018, patients aged > 18 y who were admitted within 24 h of the burn incident at the burn intensive care unit (BICU) of Hangang Sacred Heart Hospital, Hallym University Medical Center were included in this retrospective study; all the patients underwent acute fluid resuscitation during the first 3 days after the burn. The indications of admission to BICU were as follows: 1) partial thickness burn of > 20% of total body surface area (TBSA) for adults and partial thickness burn of > 10% of the TBSA in patients aged > 65 years, 2) inhalation injury, 3) electrical burn, 4) preexisting medical disorder that could incur complications or affect mortality, and 5) concomitant trauma that could elevate the risk of morbidity or mortality. Clinical longitudinal data that were measured routinely and were known predictors, such as white blood cell (WBC), platelet count, lactate (3), creatinine, total bilirubin (TB), and prothrombin time (PT) were retrieved from a clinical database warehouse at the Hangang Sacred Heart Hospital. The study period was the stay in the BICU. When the biomarkers were measured several times each day, we recorded the poorest value recorded. We also noted demographic variables, such as age, sex, TBSA (calculated by surgeon using a modified Lund and Browder chart) (4), type of burn, length of BICU stay, and presence of inhalation injury (5). The primary outcome was the ICU mortality. The severity of injury was reported using the Abbreviated Burn Severity Index (ABSI) (6), the newly developed Hangang score (7) at our center, and the Acute Physiology and Chronic Health Evaluation Score (APACHE) IV (8).

2.1. Statistical Analyses

Baseline demographic characteristics were reported as follows. Continuous, normal variables are presented as mean ± standard deviation (SD) values and non-normal variables are presented as medians (25th interquartile range [IQR] – 75th IQR). The independent-test or Wilcoxon signed rank test, depending on data normality was used to determine differences between the two groups. Categorical variables were analyzed using the Chi-square test and are presented as percentages. We used two methods of time-dependent receiver operating characteristic (ROC) curves to evaluate the time-varying prognostic performance using fixed baseline biomarkers measured at admission and updated biomarkers measured routinely during the study period. We calculated the incident/dynamic ROC using non-parametric rank-based approach, allocating subjects with an event at time into positive group and subject who experience event thereafter into negative group.(9). The cumulative/dynamic ROC curve is performed by allocating subject who experienced the event before fixed point of time into positive group and eventless subject

during time into negative group.(10) The data for cumulative/dynamic ROC was subsetted to analyze the diagnostic performance at an every week from 1 week and 8th week. Confidence intervals were calculated using 500-time bootstrap resampling, and percentile-based confidence intervals were obtained. Two side p-value < 0.05 was considered statistically significant. All analyses were conducted by using computing statistical R-project program version 3.6.

Results

3.1. Baseline Characteristics of the Survivors and Non-survivors.

Total 2259 patients were included in this retrospective study; 1786 patients were allocated to the survival group and 473 to the non-survival group; the overall mortality was 20.9%. The overall median age was 48.0 y and was higher in the non-survival group than in the survival group (52.0 vs. 46.0). The overall median burnt TBSA was 24.0%; the value was higher at 65.0% in the non-survival group. The inhalation was significantly higher at 78.2% in the non-survival group. All the severity scores were significantly higher (62.0 in APAHCHE IV, 161.0 in Hangang, 12.0 in ABSI) in the non-survival group. All baseline laboratory results included in this study were collected at admission and were significantly different between two groups (Table 1). The overall numbers of measurement for each biomarker were 43455 in platelet, WBC, 43441 in creatinine, 43438 in TB, 43182 in lactate and 43340 in PT.

Table 1
Baseline characteristics between the two groups

Variables	Survivors(n = 1786)	Non-survivors(n = 473)	Total(n = 2259)	p
age	46.0 [37.0;55.0]	52.0 [43.0;65.0]	48.0 [38.0;56.5]	0.000
Gender				0.495
- Male	1469 (82.3%)	382 (80.8%)	1851 (81.9%)	
TBSA	24.0 [14.0;37.0]	65.0 [42.0;85.0]	29.0 [17.0;48.0]	0.000
Type				0.000
- FB	1228 (68.8%)	421 (89.0%)	1649 (73.0%)	
- EB	318 (17.8%)	9 (1.9%)	327 (14.5%)	
- SB	156 (8.7%)	30 (6.3%)	186 (8.2%)	
- CoB	50 (2.8%)	10 (2.1%)	60 (2.7%)	
- ChB	34 (1.9%)	3 (0.6%)	37 (1.6%)	
Inhalation	812 (45.5%)	370 (78.2%)	1182 (52.3%)	0.000
APACHE_IV	33.0 [24.0;45.0]	62.0 [49.0;76.0]	38.0 [26.0;53.0]	0.000
Hangang	122.0 [113.0;132.0]	161.0 [149.0;177.0]	127.0 [115.0;144.0]	0.000
ABSI	7.0 [6.0; 9.0]	12.0 [10.0;14.0]	8.0 [6.0;10.0]	0.000
LOS	15.0 [6.0;35.0]	12.0 [7.0;22.0]	14.0 [6.0;32.0]	0.001
WBC	17.3 [13.0;22.7]	29.2 [20.6;37.4]	18.7 [13.7;26.0]	0.000
Platelet	-230.5 [-280.0;-186.0]	-193.0 [-269.0;-134.5]	-225.0 [-279.0;-175.0]	0.000
Creatinie	0.8 [0.6; 0.9]	1.0 [0.8; 1.4]	0.8 [0.7; 1.0]	0.000
Lactate	2.6 [1.7; 4.0]	5.6 [3.9; 7.9]	3.0 [1.9; 5.0]	0.000
TB	0.8 [0.5; 1.1]	1.1 [0.8; 1.7]	0.8 [0.6; 1.2]	0.000
PT	11.8 [10.9;12.9]	13.1 [11.8;14.9]	12.0 [11.0;13.3]	0.000

n, number; FB, Flame Burn; SB, Scald Burn; EB, Electrical Burn; ChB, Chemical Burn; CoB, Contact Burn; %TBSA burned, percentage of total body surface area burned; APACHE, Acute Physiology and Chronic Health Evaluation Score; ABSI, Abbreviated Burn Severity Index; LOS, length of hospital stay; TB, total bilirubin; PT, prothrombin time; WBC, white blood cell

3.2. Diagnostic Performance of Baseline and Updated Biomarkers over time using the ID Approach.

Incident/dynamic (ID) ROC curve are particularly well suited for assessing the performance of markers measured at a series of time points during decision-making (11). First, look over AUC using baseline biomarker (Table 2), C-index which shows overall performance of different biomarkers were the highest in lactate with 0.662 (95% confidence interval [CI], 0.614 ~ 0.673), but, the value of AUC in lactate were from 0.786 (0.760 ~ 0.812) in 1st week to 0.574 (0.509 ~ 0.639) in 8th week showing decreasing trend. Platelet which had lower c-index with 0.576 (0.546 ~ 0.605) were from 0.576 (0.535 ~ 0.617) in 1st week to 0.711 (0.643 ~ 0.779) in 8th week showing increasing trend. For updated biomarkers (Table 3), platelet show the highest c-index with 0.930(0.919 ~ 0.941) as well as the highest during all time points. PT and creatinine show over 8 c-index with 0.862 (0.843 ~ 0.881) and 0.828 (0.809 ~ 0.848), respectively. (Fig. 1)

Table 2
Time varying Performance of baseline biomarkers using ID approach (AUC with 95% CI)

	week1	week2	week3	week4	week5	week6	week7	week8	c-index
Platelet	0.576 (0.535 ~ 0.617)	0.560 (0.516 ~ 0.604)	0.574 (0.52 ~ 0.628)	0.597 (0.534 ~ 0.659)	0.566 (0.483 ~ 0.649)	0.616 (0.527 ~ 0.705)	0.669 (0.595 ~ 0.742)	0.711 (0.643 ~ 0.779)	0.576 (0.546 ~ 0.605)
Lactate	0.786 (0.760 ~ 0.812)	0.722 (0.688 ~ 0.755)	0.654 (0.605 ~ 0.703)	0.606 (0.545 ~ 0.667)	0.586 (0.504 ~ 0.668)	0.539 (0.458 ~ 0.619)	0.555 (0.484 ~ 0.625)	0.574 (0.509 ~ 0.639)	0.662 (0.633 ~ 0.69)
WBC	0.713 (0.674 ~ 0.752)	0.701 (0.665 ~ 0.737)	0.683 (0.636 ~ 0.729)	0.630 (0.556 ~ 0.703)	0.615 (0.53 ~ 0.7)	0.575 (0.488 ~ 0.662)	0.489 (0.414 ~ 0.564)	0.522 (0.453 ~ 0.591)	0.644 (0.614 ~ 0.673)
TB	0.614 (0.577 ~ 0.65)	0.589 (0.545 ~ 0.633)	0.596 (0.543 ~ 0.649)	0.577 (0.516 ~ 0.638)	0.506 (0.42 ~ 0.592)	0.467 (0.373 ~ 0.56)	0.414 (0.333 ~ 0.495)	0.448 (0.384 ~ 0.511)	0.572 (0.544 ~ 0.599)
PT	0.681 (0.647 ~ 0.715)	0.623 (0.585 ~ 0.66)	0.616 (0.565 ~ 0.667)	0.635 (0.579 ~ 0.691)	0.633 (0.571 ~ 0.694)	0.644 (0.573 ~ 0.715)	0.648 (0.578 ~ 0.718)	0.643 (0.584 ~ 0.702)	0.634 (0.607 ~ 0.661)
Creatinie	0.690 (0.655 ~ 0.725)	0.640 (0.599 ~ 0.68)	0.594 (0.539 ~ 0.649)	0.5645 (0.509 ~ 0.62)	0.561 (0.495 ~ 0.626)	0.558 (0.489 ~ 0.627)	0.506 (0.438 ~ 0.573)	0.518 (0.452 ~ 0.584)	0.615 (0.588 ~ 0.642)

CI, confidence interval; TB, total bilirubin; PT, prothrombin time; WBC, white blood cell

Table 3
Time varying Performance of updated biomarker using ID approach (AUC with 95% CI)

	week1	week2	week3	week4	week5	week6	week7	week8	c-index
Platelet	0.938 (0.922 ~ 0.954)	0.956 (0.946 ~ 0.966)	0.958 (0.941 ~ 0.975)	0.970 (0.956 ~ 0.984)	0.974 (0.96 ~ 0.988)	0.980 (0.968 ~ 0.992)	0.980 (0.968 ~ 0.992)	0.987 (0.973 ~ 1)	0.930 (0.919 ~ 0.941)
Lactate	0.801 (0.771 ~ 0.83)	0.775 (0.739 ~ 0.81)	0.810 (0.774 ~ 0.846)	0.853 (0.809 ~ 0.897)	0.868 (0.82 ~ 0.916)	0.901 (0.854 ~ 0.948)	0.909 (0.858 ~ 0.96)	0.922 (0.873 ~ 0.97)	0.786 (0.758 ~ 0.814)
WBC	0.653 (0.616 ~ 0.69)	0.707 (0.675 ~ 0.739)	0.753 (0.709 ~ 0.796)	0.813 (0.763 ~ 0.862)	0.817 (0.748 ~ 0.886)	0.770 (0.691 ~ 0.849)	0.714 (0.618 ~ 0.809)	0.703 (0.609 ~ 0.797)	0.684 (0.658 ~ 0.711)
TB	0.745 (0.713 ~ 0.777)	0.820 (0.795 ~ 0.845)	0.910 (0.888 ~ 0.932)	0.937 (0.912 ~ 0.962)	0.900 (0.849 ~ 0.950)	0.897 (0.841 ~ 0.952)	0.910 (0.858 ~ 0.961)	0.946 (0.908 ~ 0.983)	0.782 (0.757 ~ 0.807)
PT	0.872 (0.850 ~ 0.894)	0.871 (0.848 ~ 0.894)	0.905 (0.881 ~ 0.929)	0.933 (0.908 ~ 0.957)	0.900 (0.846 ~ 0.953)	0.897 (0.834 ~ 0.96)	0.898 (0.835 ~ 0.961)	0.950 (0.917 ~ 0.982)	0.862 (0.843 ~ 0.881)
Creatinie	0.873 (0.850 ~ 0.895)	0.876 (0.854 ~ 0.897)	0.838 (0.805 ~ 0.871)	0.813 (0.761 ~ 0.864)	0.733 (0.653 ~ 0.813)	0.726 (0.634 ~ 0.818)	0.666 (0.568 ~ 0.764)	0.715 (0.626 ~ 0.803)	0.828 (0.809 ~ 0.848)

CI, confidence interval; TB, total bilirubin; PT, prothrombin time; WBC, white blood cell

3.3. Diagnostic Performance of Baseline and Updated Biomarkers over time by CD Approach.

Cumulative/dynamic (CD) ROC curves are suitable tool for assessing prognostic accuracy when interested in identifying individuals at risk of event before time of interest.(11) We set time of interest as 1 week. First, look over AUC using baseline biomarker, (Table 4) the value of AUC in platelet were from 0.562 (0.504 ~ 0.62) in 1st week to 0.888 (0.829 ~ 0.946) in 8th week showing increasing trend. Lactate were from 0.756 (0.714 ~ 0.798) in 1st week to 0.550 (0.356 ~ 0.743) in 8th week showing decreasing trend. For update biomarkers (Table 5), platelet show the highest value of AUC 0.871 (0.841 ~ 0.900) in 1st week and 0.999 (0.997 ~ 1.000) in 8th week. Lactate show the highest value of AUC with 0.999 (0.998 ~ 1.000) in 7th week, PT show the value of over 7 except week 6 (0.566, 95%CI 245 ~ 0.887) (Fig. 2).

Table 4
Time varying Performance of baseline biomarkers using CD approach (AUC with 95% CI)

	week1	week2	week3	week4	week5	week6	week7	week8
Platelet	0.562 (0.504 ~ 0.620)	0.570 (0.496 ~ 0.643)	0.611 (0.531 ~ 0.691)	0.622 (0.507 ~ 0.737)	0.514 (0.351 ~ 0.677)	0.605 (0.401 ~ 0.808)	0.857 (0.793 ~ 0.920)	0.888 (0.829 ~ 0.946)
Lactate	0.756 (0.714 ~ 0.798)	0.710 (0.649 ~ 0.77)	0.623 (0.555 ~ 0.691)	0.600 (0.486 ~ 0.713)	0.592 (0.412 ~ 0.772)	0.469 (0.289 ~ 0.649)	0.409 (0.223 ~ 0.594)	0.550 (0.356 ~ 0.743)
WBC	0.689 (0.632 ~ 0.745)	0.679 (0.608 ~ 0.749)	0.612 (0.519 ~ 0.705)	0.618 (0.506 ~ 0.73)	0.603 (0.435 ~ 0.77)	0.511 (0.29 ~ 0.731)	0.427 (0.284 ~ 0.570)	0.263 (0.073 ~ 0.452)
TB	0.617 (0.567 ~ 0.667)	0.599 (0.523 ~ 0.674)	0.654 (0.572 ~ 0.736)	0.612 (0.513 ~ 0.711)	0.421 (0.23 ~ 0.612)	0.483 (0.285 ~ 0.68)	0.512 (0.375 ~ 0.649)	0.489 (0.303 ~ 0.674)
PT	0.635 (0.583 ~ 0.687)	0.596 (0.532 ~ 0.660)	0.596 (0.515 ~ 0.676)	0.659 (0.569 ~ 0.748)	0.637 (0.484 ~ 0.789)	0.564 (0.406 ~ 0.722)	0.672 (0.577 ~ 0.767)	0.674 (0.533 ~ 0.814)
Creatinie	0.648 (0.597 ~ 0.699)	0.633 (0.567 ~ 0.699)	0.573 (0.493 ~ 0.653)	0.574 (0.480 ~ 0.668)	0.587 (0.428 ~ 0.745)	0.540 (0.315 ~ 0.764)	0.601 (0.443 ~ 0.758)	0.276 (0.215 ~ 0.336)

TB, total bilirubin; PT, prothrombin time; WBC, white blood cell

Table 5
Time varying Performance of updated biomarker using CD approach (AUC with 95% CI)

	week1	week2	week3	week4	week5	week6	week7	week8
Platelet	0.871 (0.841 ~ 0.900)	0.923 (0.899 ~ 0.946)	0.944 (0.922 ~ 0.966)	0.788 (0.694 ~ 0.881)	0.989 (0.979 ~ 0.999)	0.655 (0.445 ~ 0.864)	0.953 (0.913 ~ 0.992)	0.999 (0.997 ~ 1.000)
Lactate	0.699 (0.657 ~ 0.741)	0.756 (0.692 ~ 0.819)	0.867 (0.83 ~ 0.904)	0.729 (0.648 ~ 0.81)	0.991 (0.983 ~ 0.999)	0.787 (0.669 ~ 0.904)	0.999 (0.998 ~ 1.000)	0.938 (0.887 ~ 0.989)
WBC	0.572 (0.517 ~ 0.627)	0.615 (0.540 ~ 0.689)	0.679 (0.585 ~ 0.773)	0.695 (0.589 ~ 0.800)	0.994 (0.989 ~ 0.999)	0.897 (0.818 ~ 0.975)	0.532 (0.228 ~ 0.836)	0.659 (0.391 ~ 0.927)
TB	0.595 (0.543 ~ 0.647)	0.686 (0.628 ~ 0.743)	0.822 (0.768 ~ 0.875)	0.746 (0.664 ~ 0.827)	0.982 (0.971 ~ 0.992)	0.438 (0.113 ~ 0.763)	0.935 (0.893 ~ 0.977)	0.960 (0.926 ~ 0.994)
PT	0.737 (0.693 ~ 0.781)	0.719 (0.654 ~ 0.783)	0.775 (0.719 ~ 0.83)	0.730 (0.615 ~ 0.844)	0.983 (0.973 ~ 0.992)	0.566 (0.245 ~ 0.887)	0.975 (0.952 ~ 0.998)	0.841 (0.761 ~ 0.921)
Creatinie	0.850 (0.815 ~ 0.885)	0.811 (0.736 ~ 0.885)	0.850 (0.792 ~ 0.908)	0.599 (0.498 ~ 0.699)	0.861 (0.827 ~ 0.895)	0.288 (0.201 ~ 0.375)	0.652 (0.337 ~ 0.967)	0.525 (0.367 ~ 0.683)

TB, total bilirubin; PT, prothrombin time; WBC, white blood cell

Discussions

We evaluated time-varying diagnostic performance of biomarkers measured at admission only and updated the biomarkers at several time points in routine clinical setting. The performance of updated biomarkers by ID approach was higher than the baseline biomarkers in all situations with the exception of 1st (0.713 vs. 0.653) week in WBC (Table 1 ,2). The performance of updated biomarkers by CD approach was higher than the baseline biomarker in most parameters except lactate in 1st week (0.756 vs. 0.699), 1st (0.689 vs. 0.572), 2nd (0.679 vs. 0.615) week in WBC, 1st (0.617 vs. 0.595), 6th (0.483 vs. 0.438) in TB, 6th (0.540 vs. 0.288) in creatinine (Table 4,5). From the results, we identified that patient biomarkers must be regularly updated to maintain prognostic accuracy because good prognostic markers effectively suggest the choice and timing of therapeutic interventions, allowing timely action for individuals with the greatest risk of complications.

The updated platelet had the highest c-index of 0.930 (95% CI, 0.919–0.941), which keeps the AUC I/D over 0.930 over time, indicating a strong prognostic biomarker for practical use. Moreover, we used AUC C/D over a period of 1 wk to actually evaluate the use of updated biomarkers as a decision tool. We found that AUC C/D of platelet was consistently higher than 0.870 at all the selected time points except at week 4 and 6. This indicates that platelet identifies high-risk patients at high-risk for mortality. Cate et al. (12) reported that platelet count is a strong predictor of mortality and showed AUC (0.779, 95% CI 0.697–0.862) that were calculated by the value measured on the 3rd day after admission. Huang et al. (13) reported platelets well discriminated mortality and showed AUC 0.782. Lactate has been used as a predictor by checking cellular hypoxia and shock and was reported that showed high prognostic performance of AUC with 0.82 (14). Adding lactate to severity scores predicts mortality better in critical ill patients. (15) In our study, lactate showed a relatively lower c-index with 0.786 than platelets, PT, and creatinine. We infer that this could be because lactate further reflects the severity of the burn than mortality. Creatinine is also a better risk factor of acute kidney injury (AKI) rather than mortality (16). However, creatinine showed high discrimination with c-index of 0.828. This is probably because AKI is one of the most common complications in burn patients. PT showed high c-index of 0.862 because PT was reported as a predictor in many diseases, such as liver disease, cardiac disease, and trauma (17–19). PT is reported to be an early predictor due to hepatic dysfunctions (20). However, PT was a good predictor throughout the period.

There are certain limitations of this study. First, it was not multicenter study; thus, our population does not represent the entire population of Korea. However, our center is the only unit run by the University in Korea. Second, we set an arbitrary window period of 1 wk for CD approach to compare the biomarkers and thus cannot conclude how often the biomarkers should be updated.

Conclusions

To predict effectively, biomarkers should be updated regularly. Platelet count showed the best prognostic performance. PT and creatinine as prognostic factors for certain disease, and the diagnostic power is good at s specific time point, however, the overall diagnostic performance is good in burn patients. Lactate is known strong predictor, but showed relatively low prognostic performance in burn patients.

List Of Abbreviations

WBC, white blood cell; TB, total bilirubin; PT, prothrombin time; ROC, receiver operating characteristic; AUC, area under the curve; ID, incident/dynamic; ICU, intensive burn unit; AKI, acute kidney injury; BICU, burn intensive care unit; TBSA, total body surface area; ABSI, abbreviated burn severity index; APACHE, acute physiology and chronic health evaluation score; SD, standard deviation; IQR, interquartile range; n, number; FB, Flame Burn; SB, Scald Burn; EB, Electrical Burn; ChB, Chemical Burn; CoB, Contact Burn; CD, cumulative/dynamic

Declarations

Consent for publications

Not applicable in this section.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional review board of the Hangang Sacred Heart Hospital, and informed consent was waived, as this study was retrospective in nature and did not include any intervention.

Author Contributions

Conceptualization, Dohern Kym and Jun Hur; Data curation, Jaechul Yoon; Formal analysis, Yong Suk Cho; Funding acquisition, Jun Hur; Investigation, Jun Hur; Methodology, Dohern Kym; Resources, Jae Hee Won; Software, Wook Chun; Validation, Jun Hur and Haejun Yim; Writing – original draft, Jun Hur; Writing – review & editing, Dohern Kym.
All authors have read and agreed to the published version of the manuscript

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Conflicts of Interest

The authors declare no conflict of interest

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Not applicable in this section.

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Figures

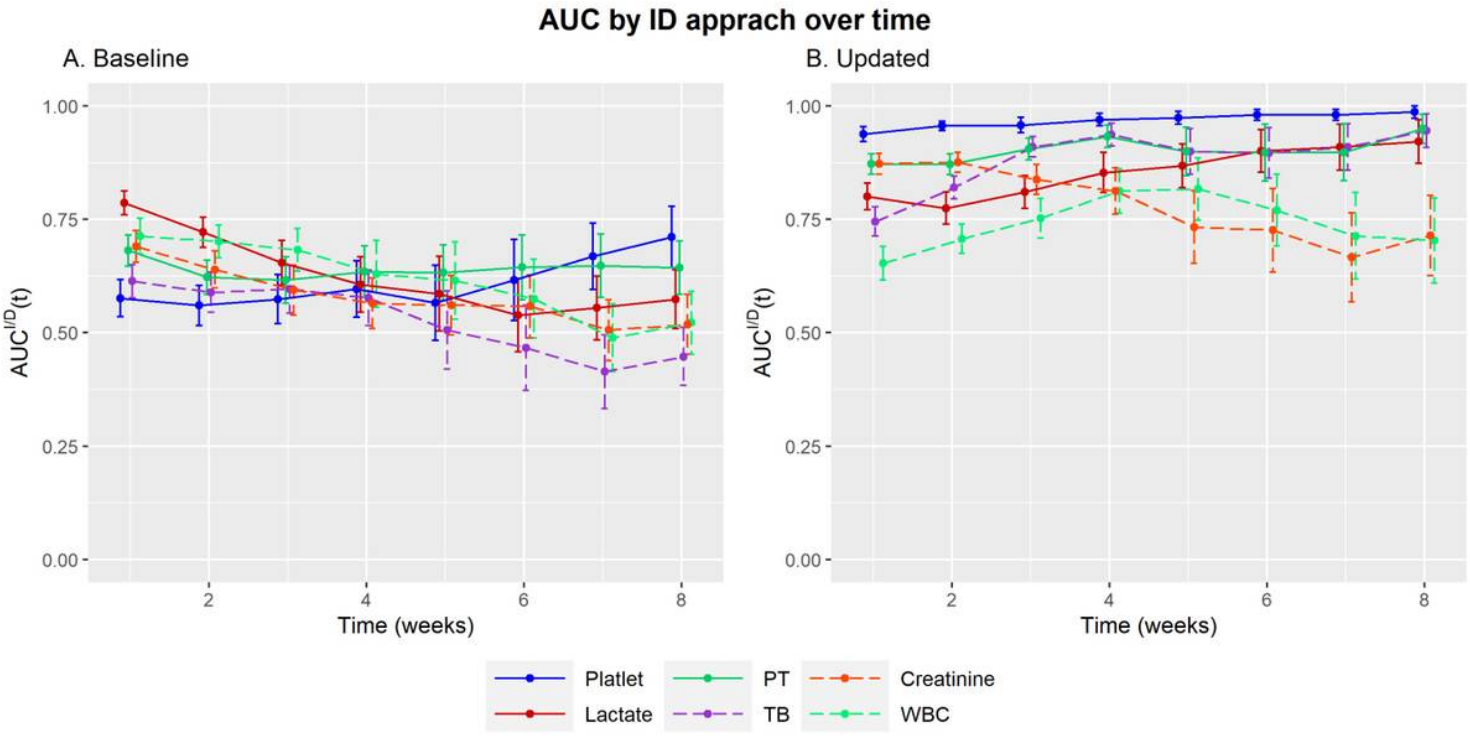

Figure 1

Diagnostic Performance of Baseline and Updated Biomarkers over time using the ID Approach. Error bar is 95%d confidence interval calculated by bootstrap.

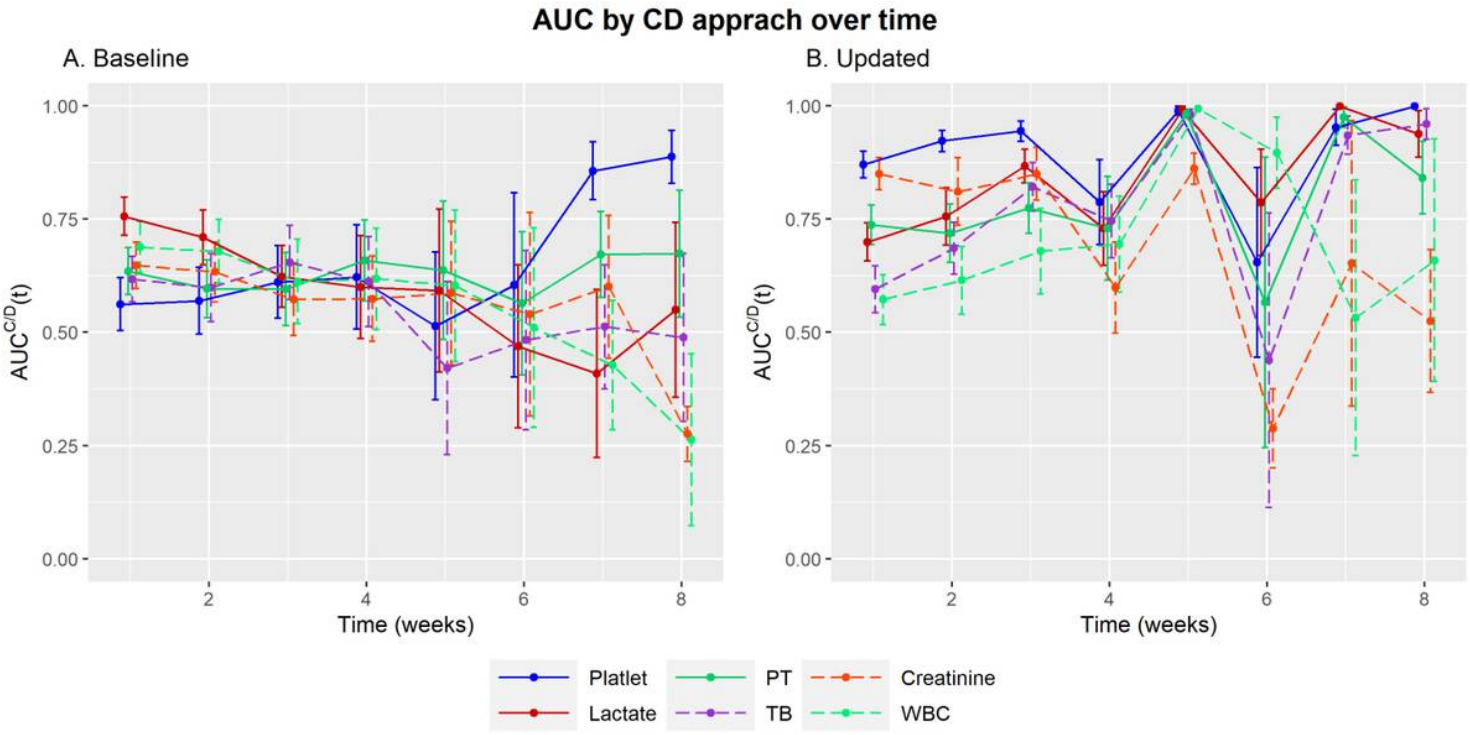

Figure 2

Diagnostic Performance of Baseline and Updated Biomarkers over time by CD Approach. Error bar is 95%d confidence interval calculated by bootstrap