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ORIGINAL ARTICLE

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Biomarkers for the early detection of pressure ulcers in the intensive care setting: A comparison between sub-epidermal moisture measurements and interleukin-1α

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Abstract

Pressure ulcer (PU) prevention in the intensive care unit (ICU) is an important clinical issue as critically unwell patients are at high risk of developing PUs. However, current methods of PU detection are limited, especially for early detection. This study aimed to establish the correlation between Interleukin-1α (IL-1α)/total protein (TP) and sub-epidermal moisture (SEM) measurements in the early identification of PUs in ICU patients. This study employed an observational research design using the STROBE guidelines. Following ethical

approval, 53 participants were recruited and sebum was obtained using Sebutape from weight-bearing areas (sacrum, heels and a control site). SEM measurements were taken from the same anatomical sites. Both measures were taken at the same time and participants were followed up for 5 days, or until discharge or death. Correlations between SEM delta measurements, IL-1α, TP and PU incidence and other demographic information were explored using Spearman's correlation for data not normally distributed, and Pearson's *R* correlation coefficient for normally distributed data. Mean baseline SEM delta measurements indicate abnormal readings for all anatomical sites except the control site, consistent with previous studies. Mean baseline IL-1α/TP readings were higher for the sacrum versus both heels and, on average, readings were higher for the control site versus all other anatomical locations. This is conflicting, given that the control site was non-weight bearing. There were very weak or weak correlations between SEM delta measurements and IL-1α/TP readings. SEM measurements are quick and easy to obtain and results are instant, however Sebutape sampling takes significantly longer and is challenging to conduct among haemodynamically unstable patients. Obtaining SEM measurements is more practical and feasible than Sebutape sampling to assess for the presence of inflammation.

KEYWORDS

biomarkers, critical care, inflammation, pressure sore, pressure ulcer

Key Messages

- The current gold standard of pressure ulcer (PU) detection involves visual skin assessment (VSA); reliance on VSA as a method of PU detection is problematic given that PUs' often develop from within the deeper tissues at a microscopic rather than macroscopic level
- Further research into the early methods of PU detection are needed to facilitate an objective approach to diagnosis, which can inform the implementation of prevention strategies to prevent progression of PUs
- In this study, it was found that there was a weak correlation between subepidermal moisture (SEM) delta measurements and interleukin-1α/total protein readings; furthermore, obtaining SEM measurements is more practical and feasible than Sebutape sampling to detect PUs

1 | INTRODUCTION

Pressure Ulcer (PU) prevention among critically unwell patients admitted to the intensive care unit (ICU) is an important clinical issue as these patients are at high risk of developing PUs.[1] ICU patients have the highest rates of hospital acquired PUs as a result of their severity of illness, combined with immobility and treatment interventions.[2-5] The annual incidence of PUs in ICUs in the United States (US) is 12% to 42%, equating to an estimated $1.99 billion in expenditure associated with prevention and treatment.[2-4] The impact of PUs in this particularly vulnerable cohort of patients must not be underestimated. Patients who develop PUs often experience pain, depression, loss of independence and additional surgical procedures all of which have the potential to lead to prolonged hospitalisation.[3]

Current methods of PU detection are limited. The current gold standard of PU assessment involves visual skin assessment (VSA).[6] Reliance on VSA as a method of PU detection is problematic given that PUs often develop from within the deeper tissues.[7] As such, VSA is not sufficient to detect damage until skin changes are visually apparent on the skin surface.[8] If methods of early detection are not improved upon, PU incidence and prevalence is unlikely to

reduce substantially. Further research into the early methods of PU detection is needed to facilitate an objective approach to PU diagnosis, thus leading to the implementation of prevention and treatment strategies in a timely manner.

Cytokines are synthesised and released when mechanical injury of the skin cells occurs, making them a biomarker. An example of a pro-inflammatory cytokine is IL-1α, which is released after injury to the keratinocytes. Studies have demonstrated that IL-1α is significantly increased after pressure loading of the skin.[9] A method has been developed to collect samples for IL-1α and TP non-invasively using Sebutape. These tapes are commercially available (Cu-Derm, Dallas, Texas), and can acquire sebum non-invasively by applying it to the skin surface in the region of interest for a period of 2 minutes. Sebum is an oily substance found on the skin surface and is a product of the sebaceous glands.[10]

In recent years a new technology, based on the principles of capacitance, has been CE marked for the early detection of skin and subdermal changes based on the principles of inflammation. The SEM Scanner was developed by Bruin Biometrics and is a hand-held, portable, device. The device is placed over an anatomical site, such as the sacrum and heels. The moisture level of the sub-epidermal tissue is measured using electrode structures placed on the surface of the skin. Low amplitude signals use surface electrical capacitance to assess the level of fluid in the epidermal and subepidermal tissues. Fluid in the tissue is part of the inflammation process that happens when PUs are forming. To date, a comparison of Sebutape and SEM measurements as early determinants of PU formation has not been made. Research is ongoing in the areas of SEM, and the detection of biomarkers and cytokines using Sebutape as early determinants of PU development. It could be hypothesised that if both measures are exploring the same concept, that is, early PU development, then it is reasonable to expect that there would be a relationship between these measurements. However, at present, this remains unknown. This study was focussed on addressing this research gap. The purpose of this study was to determine the correlation between interleukin-1α (IL-1α) and total protein (TP) and subepidermal moisture (SEM) measurements in the early detection of PUs in adult ICU patients.

2 | METHODS

2.1 | Study aim

The overarching aim of this study was to establish the correlation between IL-1α/TP and SEM measurements in the early identification of PUs in adult intensive care patients.

2.2 | Study design

This study used an observational research design following the STROBE guidelines.[11]

2.3 | Study setting

This study was conducted in the ICU of a large tertiary hospital in the Republic of Ireland comprising a total of 23 ICU beds.

2.4 | Ethical considerations

Ethical approval was granted from the hospital site (#19/36). A declaration was granted by the Health Research Consent Declaration Committee (HRCDC) of Ireland. Participants were recruited to the study using a next-of-kin assent model developed in conjunction with and approved by the HRCDC and the Research Ethics Committee. In the event that a participant regained capacity, the Researcher obtained written informed consent from each subject to continue in the study.

2.5 | Sample size

The sample size was explored in terms of the primary objective to investigate the correlation between SEM measurements and IL-1α/TP levels. Identifying a moderate to strong correlation (i.e., $-0.4 \leq$ or ≥ 0.4) was considered clinically relevant. To detect a correlation of ≥ 0.4 or ≤ -0.4 using a two-sided test, 5% significance level test ($\alpha = .05$) with 80% power, the required sample size was approximately 47. With a sample size of approximately 50, a two-sided test, 5% significance level test, gives 90% power to detect a correlation of approximately ≥ 0.45 or ≤ -0.45.

2.6 | Study population

The population of interest in this study was ICU patients. A number of healthy volunteers were also recruited to the study to allow comparison of results from ICU participants against healthy controls.

2.7 | Eligibility criteria

To be eligible for inclusion in this study patients must have met all of the inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Patients admitted to an ICU
- Patients without existing PUs
- Patients who consented to participate or were assented by their next of kin
- Over 18 years of age

Exclusion criteria

- Patients not admitted to an ICU
- Patients with existing PUs
- Patients who did not consent to participate
- Patients who were not assented by their next of kin
- Under 18 years of age
- Patients who are too haemodynamically unstable to reposition

2.8 | Variables

PU risk assessment was completed on all patients at baseline using the Braden scale.[12] In this study VSA, SEM measurements and Sebutape sampling were undertaken at each study visit. The European Pressure Ulcer Advisory Panel (2019) classification system was used to grade PUs.[13] SEM delta values were assessed using the SEM Scanner. For the assessment of each anatomical site, the difference between the highest and the lowest reading provides the delta which is the number of interest.[14] A SEM reading ≥0.5 was considered high or abnormal which is the cut-off point used in previous studies.[15] Sebutape was used to collect sebum non-invasively to quantify IL-1α and TP. Demographic information (name, gender and age) was collected so that the researcher could make sure participants were followed up for the duration of the study. Other relevant clinical data obtained included blood results collected as part of standard of care in ICU. C-reactive protein (CRP) was measured daily on included participants. CRP is an acute inflammatory protein that increases significantly at sites of infection or inflammation.[16] The purpose for recording CRP values in this study was to determine if there was a correlation between systemic inflammation measured by circulatory CRP and localised inflammation using Sebutape to measure IL-1α/TP. A predesigned data collection document was used in this study to document all relevant variables.

2.9 | Study visit protocol

Once patients were eligible for inclusion and consent was obtained to participate, patients were enrolled to the study. Patients were visited once daily for five consecutive days. The SEM Scanner was used to record SEM delta measurements of the skin on the sacrum, both heels and a control site (anterior aspect of the head of the humerus). A control site is an area of the body where there was no pressure applied. Sebutape was then applied to the same anatomical sites (heels, sacrum and a control site). Sebutape was applied to the skin using a forceps and left in situ for 2 minutes and removed using a forceps. The Sebutape was inserted into a 2 mL tube using the forceps, ensuring that the sticky side was not touching the surface of the tube. The tube was labelled with patient number and skin site ensuring no personally identifiable information was written on the tube. Day of study visit was also documented. A tissue culture grade permanent pen was used. The tube containing Sebutape was placed immediately transported for storage in a −80° freezer.

2.10 | Biochemical analysis protocol

An amended version of a protocol devised by Perkins et al was used to quantify IL-1α levels.[17] In summary, 1.7 mL of phosphate buffered saline (PBS) and 0.05% TWEEN was added to each 2 mL tube containing Sebutape. Tubes containing Sebutape and PBS/TWEEN were left for 1 hour. After immersion for 1 hour, the tapes were sonicated for 10 minutes in a sonic water bath. Samples were vortexed for 2 minutes. Samples were refrozen overnight at −80°. To measure IL-1α, samples were thawed and levels were measured by ELISA (R&D systems, Minneapolis, Minnesota) in accordance with the manufacturer's instructions. In addition, TP concentration in the Sebutape samples was determined using a colorimetric Micro BCA Protein Assay Kit (Product No. 23235, Thermo Fisher Scientific, USA), which allowed for normalisation of the readings of IL-1α.

2.11 | Data analysis

Descriptive statistics are presented using counts and percentages, means and their associated standard deviations. Normality of the data was assessed using the Shapiro-Wilk test. Correlations between the population in terms of SEM, IL-1α and TP and PU incidence, and other demographic information were explored using Spearman's correlation (R_s) where the data were not normally distributed, and Pearson's R correlation coefficient where the data were normally distributed. Statistical significance was set at $P \leq .05$. Data analyses were performed using the statistical software Statistical Package for Social

Sciences (SPSS) by IBM for Windows version 27 and Stata by Stata Corp for Windows version 16.

3 | RESULTS

3.1 | Demographic and clinical variables

Fifty-three participants were recruited to the study. 72% (n = 38) were male and 28% (n = 15) were female. The mean age of participants was 58 years (min 20 years; max: 90 years; SD: 17 years). The mean weight of participants was 75 kg (min 50 kg; max 112 kg; SD: 11 kg). In terms of continence status, 75% (n = 40) were faecally incontinent, whilst none were urinary incontinent because of the presence of a urinary catheter.

Blood CRP results within the clinical notes were obtained from each of the study participants. Mean CRP levels were 97.37 mg/L (min 6; max 385.3; SD: 103.84). Normal CRP levels range from 0.0 to 0.5 mg/L, meaning that all CRP levels measured in all the study participants were above the normal range.

3.2 | PU risk assessment

The mean score for all of the included participants on the Braden Scale[12] was 10.2 (min 7; max 18; SD: 2.6). 81% (n = 43) of participants were deemed to be at very high/high risk of PU development.

3.3 | Baseline measurements

In this study a SEM delta of ≥0.5 was considered abnormal. The mean baseline SEM delta for the right heel was 0.72 (min: 0.2; max: 1.9; SD: 0.37), mean for the left heel was 0.74 (min: 0.2; max: 1.9; SD: 0.33), mean SEM delta for the sacrum was 0.94 (min: 0.3; max: 2.2; SD: 0.49) and mean SEM delta for the control site was 0.2 (min: 0; max: 0.5; SD: 0.12). These results indicate abnormal SEM deltas for all anatomical sites except the control site, where the reading was considered normal.

Mean baseline IL-1α reading for the for the right heel was 166.8 (min: 0.9; max: 1103; SD: 208.3), left heel was 153 (min: 8.2; max: 781; SD: 162.9), sacrum was 217.4 (min: 6.7; max: 703.4; SD: 176.2) and for the control site was 277.4 (min: 19.95; max: 829.6; SD: 229.7). Mean baseline IL-1α/TP readings for the right heel was 1.7 (min: 0.6; max: 6.7; SD: 1.6), left heel was 1.9 (min: 0.2; max: 8.8; SD: 1.8), the sacrum was 5.2 (min: 0.1; max: 23.8; SD: 5.1) and the control site was 8.9 (min: 1.2; max: 30.8; SD: 7.1). Baseline measurements for these variables can be found in Figure 1.

3.4 | Visual PU developed

A total of three participants developed a PU, and one of these participants developed two PUs. Thus, the incidence of PU development was 6% (n = 3/53). The anatomical location of the PUs was as follows, 1 right heel, 1 left heel and 2 sacral PU. All the visual PUs were assessed as being grade 1. The presence of PUs at other anatomical locations was assessed. A total of 4 participants developed another PU, yielding an incidence of other PU of 8% (n = 4/53). Of these PUs, 1 was located on each of the following anatomical locations, ankle, occiput, penile tip and the ear. Further, 3 PUs were grade 2 and 1 was a grade 4 (located on the occiput). Thus, the overall PU incidence in this study was 13% (7/53).

3.5 | SEM measurements

A total of 732 SEM delta measures were taken, 183 for each measure from each anatomical location, right heel, left heel, sacrum and control site. Overall, the mean SEM deltas were as follows: right heel 0.73 (SD: 0.32), left heel 0.73 (SD: 0.33), sacrum 0.85 (SD: 0.41) indicating abnormality and control 0.20 (SD: 0.11) indicating normality. On average, SEM delta measurements were abnormal over the study follow up period for the right heel, left heel and sacrum. However, on average, SEM delta measurements were normal over the study follow up period for the control site. Box and Whisker plots for SEM delta measurements across each study day can be found in Figure 2A-E. In these figures, data are presented as median values with minimum and maximum ranges. These plots give a visual representation of the SEM delta measurements over the study period, indicating consistently lower readings over the control site.

3.6 | SEM PU developed

A SEM PU was defined as a SEM delta of ≥0.5 for 2 or more consecutive days. A total of 10 participants developed a 14 SEM PUs during the study yielding an incidence SEM PU of 19% (n = 10). Of these, 50% (n = 7/14) were on the right heel, 21% (n = 3/14) were on the left heel and 29% (n = 4/14) were on the sacrum.

3.7 | IL-1α/TP readings

A total of 732 IL-1α/TP measures were taken, 183 for each measure from each anatomical location, right heel, left heel, sacrum and control site. Overall, the mean IL-1α/TP reading

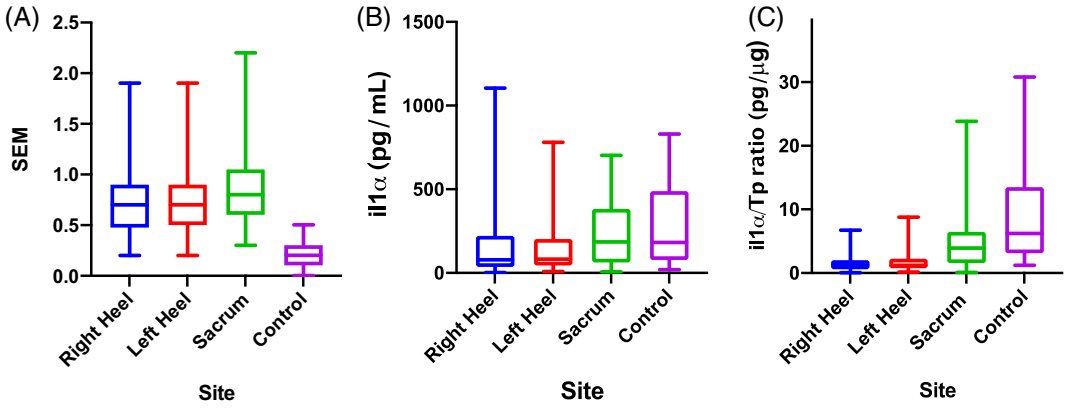

FIGURE 1 Baseline measurements. (A) Baseline sub-epidermal moisture delta measurements. (B) Baseline IL-1α (pg/mL). (C) Baseline IL-1α/total protein (pg/μg) levels

at the right heel was 1.83 (SD: 1.90), left heel 1.9 (SD: 1.54), sacrum 5.5 (SD: 5.27) and control 8.8 (SD: 7.47). Unlike SEM delta measurements, there is no normal or abnormal range or cut off point for IL-1α/TP. On average, IL-1α/TP readings were higher over the study follow up period for the sacrum versus the right heel and left heel. Further, on average, IL-1α/TP readings were higher over the study follow up period for the control site versus all other anatomical locations. Box and Whisker plots for IL-1α/TP readings across each study day can be found in Figure 3A-E. In these figures, data is presented as median values with minimum and maximum ranges. These plots give a visual representation of the readings over the study period, indicating consistently higher readings over the control site.

3.8 | IL-1α readings

Overall mean IL-1α readings at the right heel were 140.7 (SD: 154.9), left heel 153.1 (SD: 132.8), sacrum 211.7 (SD: 176.6) and control 264.2 (SD: 235.5). The mean control IL-1α reading was higher than those of any of the other anatomical sites. The results for IL-1α readings by anatomical site, by study day, are presented in Figure 4A-E. As can be seen, on average, IL-1α readings were higher over the study follow up period for the sacrum versus the right heel and left heel. Further, on average, IL-1α readings were higher over the study follow up period for the control site versus all other anatomical locations.

3.9 | Results of correlation analysis

Correlation analysis was undertaken to explore the relationship between SEM delta measurements and IL-1α/TP readings, SEM delta measurements and Blood CRP, IL-1α/TP and Blood CRP and IL-1α and SEM delta measurements.

3.9.1 | SEM delta measurements and IL-1α/TP readings

There was very weak or weak correlations between SEM delta measurements and IL-1α/TP readings at baseline for all anatomical locations (Figure 5). Further, there was weak or very weak correlations between SEM delta measurements and IL-1α/TP readings on all subsequent study days, for all anatomical locations (Table 1). In addition, these correlations were not statistically significant.

3.9.2 | SEM delta measurements and blood CRP

There was very weak or weak correlation between SEM delta measurements and Blood CRP readings on all the study days, for all the anatomical locations. Further, these correlations were not statistically significant (Table 2).

3.9.3 | IL-1α/TP and blood CRP

There was very weak or weak correlation between IL-1α/TP and Blood CRP readings on all study days, for all anatomical locations. Further, these correlations were not statistically significant, except for day 1, control site (Table 3).

3.10 | Healthy volunteers

3.10.1 | Demographic information

A total of five healthy volunteers were recruited to the study. Of these, 100% (n = 5) were female with a

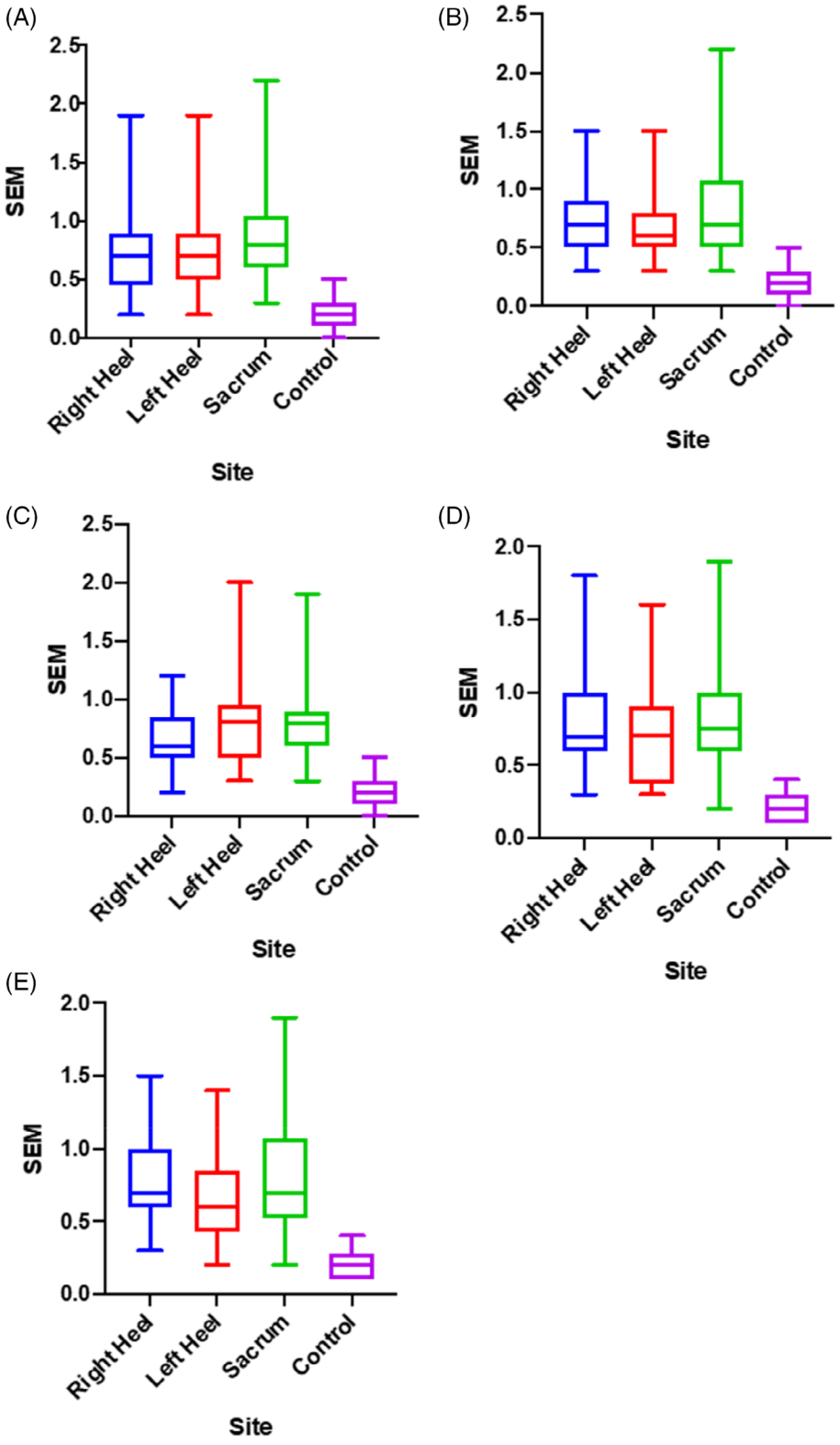

FIGURE 2 Sub-epidermal moisture delta measurements. (A) Day 1. (B) Day 2. (C) Day 3. (D) Day 4. (E) Day 5

mean age of 27.5 years (min: 27 years; max: 32 years; SD: 0.71 years) and a mean weight of 67 kg (min: 58 kg; max: 75 kg; SD: 7.7). None of the healthy volunteers had a pre-existing medical condition or an underlying comorbidity to report, and none were smokers.

3.10.2 | SEM delta measurements and IL-1α/TP readings

Mean SEM delta measurements and IL-1α/TP readings for the healthy volunteers can be found in Table 4.

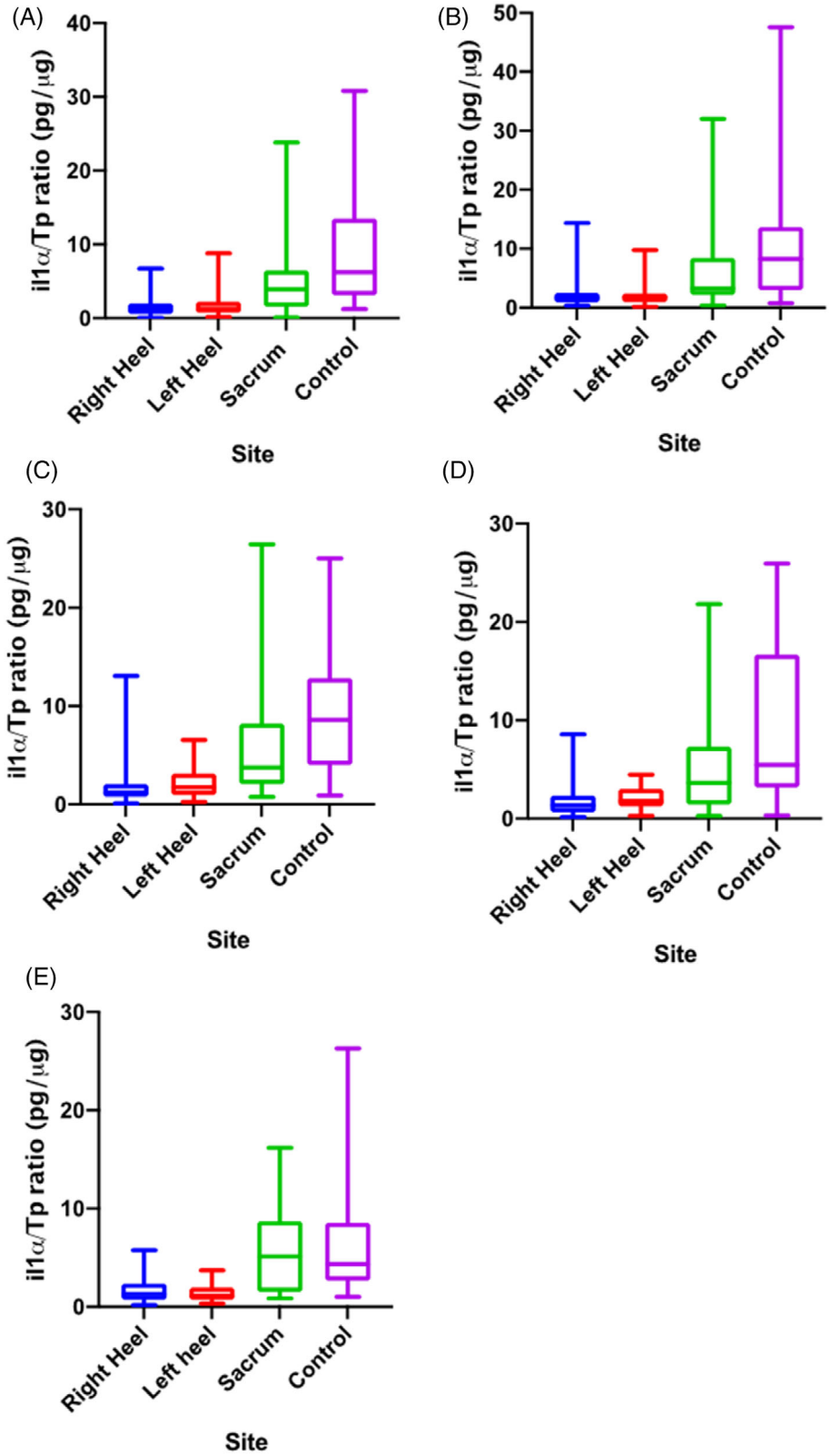

FIGURE 3 IL-1α/total protein readings. (A) Day 1. (B) Day 2. (C) Day 3. (D) Day 4. (E) Day 5

Mean SEM delta measurements were within the normal range for all sites. Mean IL-1α/TP readings were higher at the sacrum compared with both heels, and higher at the control site compared with all other sites, a similar trend to that seen among the ICU participants.

3.10.3 | Mean difference in SEM delta and IL-1α/TP measurements in healthy volunteers versus ICU participants

There was a statistically significant mean difference in SEM delta measurements, for the right heel, left heel and

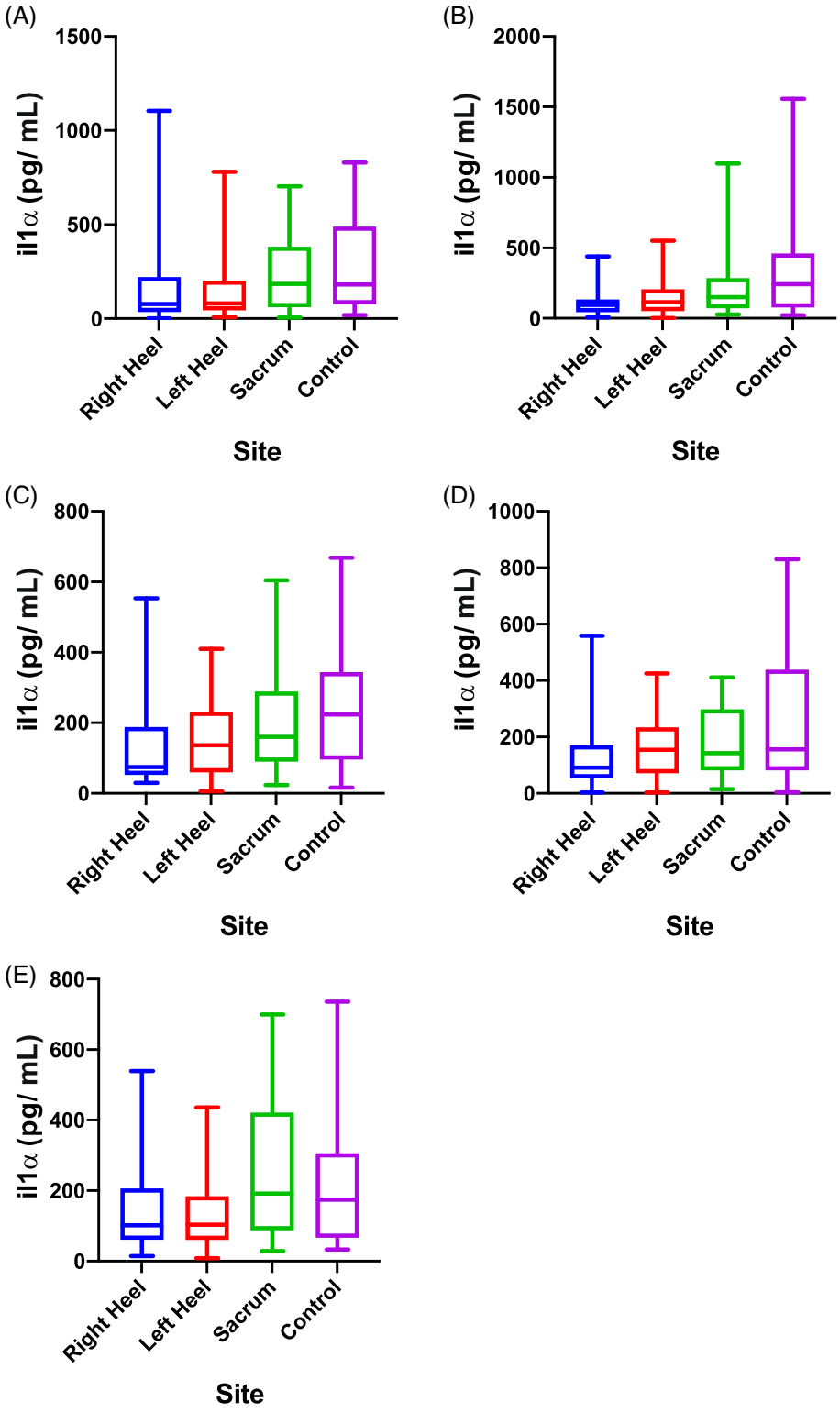

FIGURE 4 IL-1α readings. (A) Day 1. (B) Day 2. (C) Day 3. (D) Day 4. (E) Day 5

sacrum, with the ICU participants displaying higher mean measurements on average, compared with the healthy volunteers ($P < .05$). No statistically significant mean difference was noted for the control site ($P > .05$). There was also a statistically significant mean difference in IL-1α/TP readings for the right heel, left heel and control site ($P < .05$), with the ICU participants displaying higher mean scores, on average, compared with the healthy volunteers. No statistically significant mean difference was noted for the sacrum ($P > .05$).

4 | DISCUSSION

This study aimed to determine the correlation between IL-1α/TP and SEM delta measurements in the early

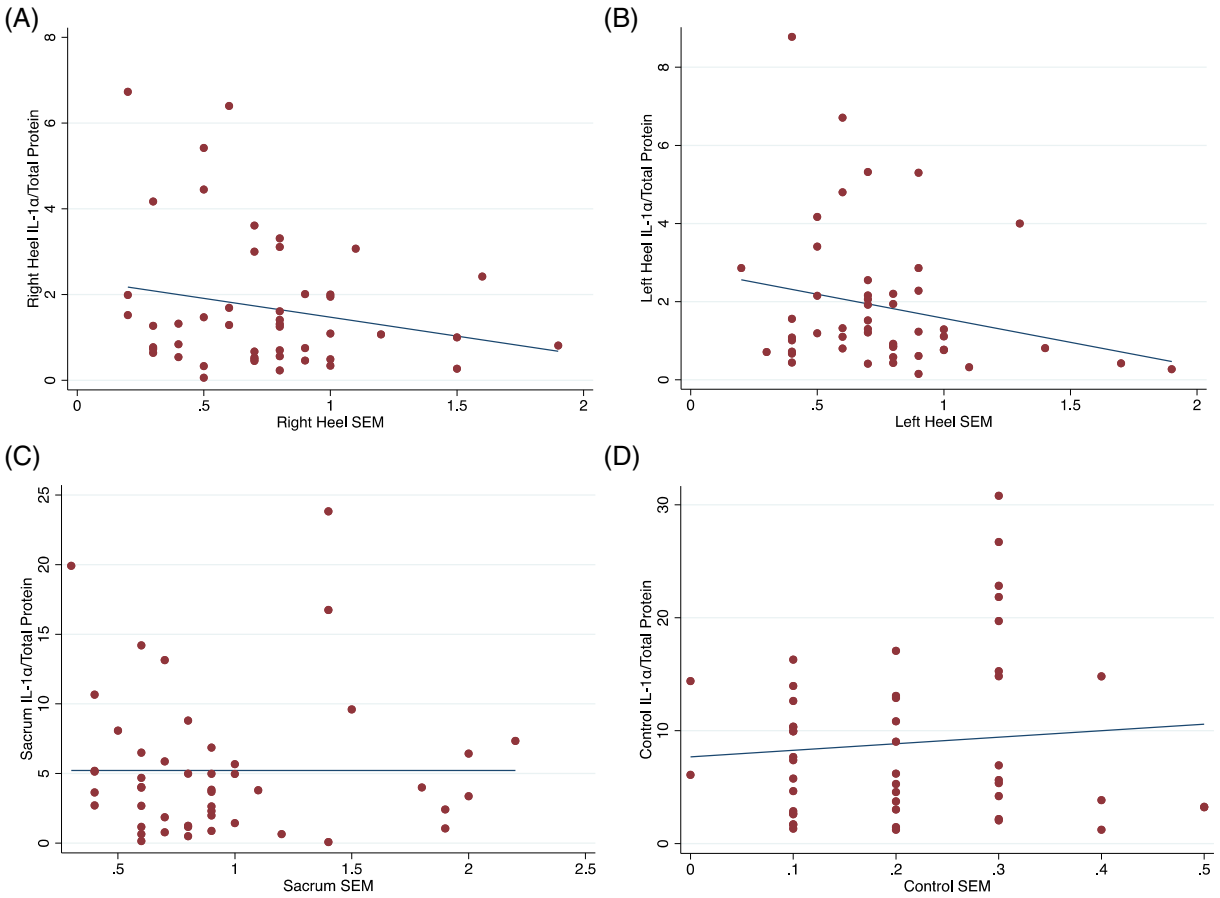

FIGURE 5 Scatterplot of sub-epidermal moisture delta measurements and IL-1α/total protein readings. (A) Right heel. (B) Left heel. (C) Sacrum. (D) Control. *Y-axis denotes varying values of IL-1α/total protein.

identification of PUs in adult intensive care patients. Results show very weak or weak correlations between SEM delta measurements and IL-1α/TP readings for all study days and all anatomical locations. There are a number of potential reasons for these results which will now be explored.

One possibility is that SEM is a measure of localised inflammation, while IL-1α/TP readings, while measured locally, can also be elevated as a result of a systemic inflammatory response. In the present study, CRP was routinely measured as part of standard care in the ICU. Levels were collected daily, and correlation analysis was undertaken to determine if there was any statistically significant correlation between systemic inflammation measured by circulatory CRP and localised inflammation using Sebutape to measure IL-1α/TP. Although other measures of systemic inflammation are used in clinical practice, the measurement of CRP is a standard blood measure obtained each day, meaning that participants in the present study were not subject to further tests or examinations. This analysis found that there was very weak or weak correlation between IL-1α/TP and Blood C Reactive Protein readings on all study days, for all anatomical locations. This result may reflect that CRP is a measure of systemic inflammation and IL-1α/TP is measuring localised inflammation, and that these are measuring very different inflammatory processes. Therefore, the question remains surrounding the exact inflammatory process that is detected using Sebutape.

It could also be possible that both SEM and IL-1α/TP detected using Sebutape, are measures of localised inflammatory processes, but at different levels of the skin. Although SEM delta measures and IL-1α/TP levels measured using Sebutape are measuring inflammatory processes, these processes are potentially measured at very different anatomical locations, that is, they are not measuring the same inflammatory process. It is well understood that SEM is a measure of the inflammatory process at the deeper layers of the skin (beneath the epidermis). The SEM scanner sensor penetrates to a typical depth of 3 to 4 mm, through the epidermis and the dermis, reaching the superficial subcutaneous fat.[18] Meanwhile Sebutape samples involve extracting sebum from the outermost layer of the skin (stratum corneum). The Sebutape method of sampling sebum involves biomarkers at the skin surface, and these surface levels do not

TABLE 1 Correlation between sub-epidermal moisture delta measures and IL-1α/total protein readings

Anatomical location	Day	R_s	*P*
Right heel	1	−0.10	.48
	2	−0.03	.87
	3	0.11	.58
	4	0.02	.91
	5	−0.12	.59
Left heel	1	−0.18	.20
	2	−0.08	.63
	3	0.05	.76
	4	−0.23	.24
	5	−0.32	.14
Sacrum	1	−0.09	.53
	2	−0.06	.69
	3	−0.06	.72
	4	−0.23	.23
	5	−0.35	.10
Control	1	0.17	.24
	2	0.30	.06
	3	0.11	.53
	4	0.32	.09
	5	0.17	.44

TABLE 2 Correlation between sub-epidermal moisture delta measurements and blood C-reactive protein

Anatomical location	Day	R_s	*P*
Right heel	1	−0.03	.82
	2	−0.04	.80
	3	0.15	.38
	4	−0.14	.47
	5	0.19	.37
Left heel	1	−0.20	.16
	2	−0.07	.63
	3	−0.19	.25
	4	−0.03	.89
	5	0.15	.49
Sacrum	1	0.12	.40
	2	0.08	.62
	3	−0.21	.21
	4	0.09	.63
	5	0.39	.06
Control	1	−0.04	.76
	2	0.22	.15
	3	−0.14	.41
	4	−0.37	.07
	5	−0.20	.36

necessarily correspond to the ones in deeper skin layers.[19] Therefore, the results of the correlation analysis in the present study may not be entirely unexpected. It has been suggested by Bader and Worsley[20] that while cytokines, which are derived from active keratinocytes in the epidermis, may be collected from sebum at the skin surface using Sebutape, that these biomarkers provide a means to examine the status of epidermal and dermal tissues, but this provides little indication of damage to the underlying subcutaneous and muscle tissues. This limitation is important to consider given that PUs can emerge from deeper layers including skeletal muscle.[21] Thus, it remains unclear as to whether or not Sebutape has the potential to detect damage at this level and further research is needed to determine the depth of damage that can be detected using Sebutape.

One further consideration is the force and magnitude of pressure experienced by patients in the ICU when compared with healthy volunteers in previous studies. Patients are exposed to pressure and shear forces continuously, but are placed on pressure redistribution mattresses, for example, meaning that the pressure is somewhat dissipated and more evenly distributed. Meanwhile, previous studies in this area focused on healthy volunteers involving sustained pressure to one specific area of the skin.[22,23] One might suggest that the type of pressure and shear forces experienced by patients in the ICU differs to the pressure and shear forces examined in previous studies looking at non-invasive sampling of biomarkers using Sebutape. PUs can develop where there is high magnitude of pressure over a short period, or a low magnitude of pressure over long periods.[21]

Finally, levels of sebum at the skin sites of interest can also differ. In this study, it was observed that the highest levels of IL-1α/TP were found at the control site. Few studies report the processes involved in sebum quantification using the Sebutape method, and no studies report on whether IL-1α/TP levels are dependent on varying sebum concentrations at the skin sites of interest in the present study. This makes it difficult to discern if the high levels of IL-1α/TP at the control site are as a direct consequence of the amount of sebum extracted at the site, and conversely, if the low levels detected on the heels are because of low sebum uptake. It could be suggested that the amount of IL-1α/TP extracted at the sites of interest in the present study is directly proportionate to the amount of sebum on each Sebutape. In addition, the distribution of sebaceous gland throughout the

human body needs to be considered. Sebaceous glands are located in the mid-dermis, and they usually develop alongside a hair follicle. The largest and most abundant sebaceous glands are found on the face, scalp, chest and back.[24] The control site used in the present study was the anterior aspect of the head of the humerus. Arguably, there are more sebaceous glands at the shoulder compared with the heels or sacrum, and for that reason, there is more sebum excreted at the control site. Although the forearm was the control site used in previous studies, the rationale for choosing the shoulder as the control site in the present study, was because this is a bony prominence with no pressure applied. This was also the control site used in previous studies assessing SEM measurements.[15] Future studies in this area should use an alternative control site which is a bony prominence with no pressure applied.

It is also important to highlight the feasibility of using the SEM Scanner and Sebutape method of sampling sebum non-invasively to detect biomarkers. Using Sebutape in practice presented several challenges. First, unlike most previous studies using Sebutape, this study was conducted among critically unwell patients. Many of these patients were admitted to the neurosurgical ICU and were undergoing intracranial pressure (ICP) monitoring. It is a challenge to reposition patients with raised ICP levels even for short periods to assess pressure areas, without experiencing elevations in ICP levels. Measuring SEM proved to be much quicker than using Sebutape and this is important to consider when conducting future studies in this area. Another issue with Sebutape sampling was in relation to its adherence to the skin, particularly at the heels where the skin is often dry and cracked. This issue was also encountered by Bronneberg[25] where Sebutape would not adhere to the skin of the heels because of their curved surfaces and where skin folds were present.

TABLE 3 Correlation between IL-1α/total protein and blood C-reactive protein

Anatomical location	Day	R_s	P
Right heel	1	0.16	.26
	2	0.00	.98
	3	0.05	.78
	4	−0.26	.17
	5	−0.15	.50
Left heel	1	0.19	.19
	2	0.06	.69
	3	0.03	.84
	4	−0.23	.23
	5	−0.15	.50
Sacrum	1	−0.17	.23
	2	0.01	.93
	3	0.00	.98
	4	−0.28	.15
	5	−0.30	.16
Control	1	0.27	.05
	2	0.06	.69
	3	0.10	.55
	4	−0.13	.50
	5	0.03	.90

5 | LIMITATIONS

There was a high level of loss to follow up in the present study and there are several reasons for this. Participants were not followed up post ICU discharge at ward level. Future studies in the ICU could involve follow up at ward level. This may provide interesting results, potentially similar to those of O'Connor,[26] where it was found that as mobility increases, SEM delta measurements decrease. One could argue that as ICU participants are discharged to the ward, that mobility levels might increase and SEM delta measurements could decrease. Future research needs to examine this.

TABLE 4 Mean sub-epidermal moisture (SEM) delta measurements and IL-1α/total protein (TP) readings for the healthy volunteers

Measure	Anatomical location	Mean	SD	Min	Max
SEM (delta)	R heel	0.48	0.08	0.4	0.6
	L heel	0.44	0.17	0.3	0.7
	Sacrum	0.40	0.12	0.3	0.6
	Control	0.12	0.11	0	0.3
IL-1α/TP (pg/μg)	R heel	0.96	0.37	0.52	1.54
	L heel	0.68	0.38	0.27	1.15
	Sacrum	3.30	3.34	0.75	8.95
	Control	4.99	2.29	2.01	8.27

Another limitation of the present study is that only one cytokine was investigated (IL-1α) while there are many other cytokines that could be tested. According to Bronneberg[25] IL-1α in isolation is unlikely to determine the damage state of skin tissue and a combination of markers including biochemical and physiological indicators may be needed. However, previous studies investigating the effects of pressure and or shear at the skin surface using Sebutape did not yield valuable or promising results in terms of other cytokines. However, most of these studies were conducted among healthy volunteers and not among the acute patient population. Future research in this area investigating other important cytokines may yield relevant results. In addition, Bronneberg[25] expressed the needed for a multifactor biosensor and while this technology is not yet available, in the future this may prove beneficial in terms of early PU detection and objective, rather than subjective risk assessment. Soetens et al[9] also recommend a point of care biosensor capable of continuously measuring IL-1α given that current methods of assessment consume much time and are unlikely to prove practical in the clinical setting.

6 | CONCLUSION

This study involved the sampling of sebum and measurement of SEM capacitance from at PU risk skin sites in critically ill patients (sacrum, both heels and a control site). The control site was an area of the body where there is no pressure applied (anterior aspect of the head of the humerus). The findings demonstrated that there was a very weak or weak correlations between SEM delta measurements and IL-1α/TP readings on all the study days, for all anatomical locations. Further, these correlations were not statistically significant. This study has provided important information on not only the relationship between IL-1α/TP and SEM measurements as potential biomarkers in the early detection of PUs in adult ICU patients, but also sheds light on the feasibility of these methods in the ICU setting. In this study, it was found that obtaining SEM measurements was more practical and feasible than Sebutape sampling to assess for the presence of inflammation. This is fundamentally important as it is likely that future research in this area is needed, and that the results of the present study will undoubtedly inform larger scale clinical and/or laboratory-based studies.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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