ORIGINAL ARTICLE

Assessment of a prognostic biochemical indicator of nutrition and inflammation for identification of pressure ulcer risk

T M Reynolds, A Stokes, L Russell

J Clin Pathol 2006;59:308–310. doi: 10.1136/jcp.2005.029405

See end of article for authors' affiliations

Correspondence to: Professor T Reynolds, Clinical Chemistry Department, Queen's Hospital, Belvedere Road, Burton-on-Trent, Staffordshire DE13 0RB, UK; tim.reynolds@clinchem.org.uk

Accepted for publication 8 June 2005

Background: Pressure ulcers represent a major cost to the healthcare systems of the world but preventative measures are expensive and could be better targeted. Current risk screening mechanisms are often subjective and could be improved.

Aims: To evaluate whether a biochemical assessment tool (Prognostic Inflammatory and Nutritional Index; PINI) based on measurement of albumin, α 1-acid glycoprotein, C-reactive protein, and prealbumin is of value in estimating the prognosis of patients with pressure ulcers of European Pressure Ulcer Advisory Panel grade 1 and above.

Methods: Serum samples were collected from patients participating in a clinical trial of a pressure ulcer preventing mattress. These were analysed for the markers listed above and the PINI calculated. PINI was then evaluated against patient outcome.

Results: A statistically significant difference between PINI values in patients whose pressure ulcers improved and those whose ulcers worsened was found in parametric testing, but significance was not achieved in non-parametric testing. A receiver operating characteristic plot showed the PINI was superior to chance in estimating prognosis.

Conclusions: The PINI appears to offer a potential route to improving pressure ulcer risk estimation and thus allocation of scarce equipment to improve prevention.

It is well recognised that pressure ulcers represent a significant cause of morbidity and indeed mortality in elderly patients. These are particularly likely to develop in patients who are malnourished or have inflammatory conditions. This has been studied by evaluation of tissue inhibitor of matrix metalloproteinase (TIMP)-1 in patients with pressure ulcers,¹ which showed that TIMP-1 could be correlated with a score derived from two markers of malnutrition (albumin and prealbumin) and two markers of inflammation (C-reactive protein (CRP) and α 1 acid glycoprotein). The scale produced is the Prognostic Inflammatory and Nutritional Index (PINI).² However, it was linked more to the severity of inflammation/malnutrition than with the presence of ulcers.

Identification of an objective prognostic tool that could identify patients likely to develop serious pressure ulcers could be valuable. Specialised pressure reducing equipment can be expensive and consequently its availability is limited to those patients at highest risk. Risk is identified using a pragmatic scoring system (the Waterlow score), which is based on nursing assessments including the patient's history, illness, and treatment.³

The PINI works on the basis of assessment of malnutrition and inflammation. It is postulated that dermal atrophy due to reduced collagen and elastin production, combined with increased matrix metalloproteinase activity due to inflammation increases the risk of pressure ulcers.² Assessment of malnutrition is difficult,⁴ and usually relies on nursing judgement, rather than on biochemical measurements, because nurses ask the right questions on admission and are able to observe the patients' ability to feed themselves and the quantity and variety of foods they consume. Biochemical measurements should not be dismissed, however; if a suitable marker could be developed, it might prove useful in identifying "hidden" malnutrition. Of the biochemical markers of malnutrition that

have been considered, the commonest suggested is albumin. Hypoalbuminaemia is linked to protein malnutrition because the liver reduces albumin production in favour of more important plasma proteins. Other likely markers include prealbumin and retinol binding protein (RBP).⁵ None of these are without their problems; albumin can decrease because of increased vascular permeability due to disease or injury,⁶ RBP is strongly influenced by renal function,⁵ and prealbumin has a very short half life making it susceptible to recent dietary deficiencies.⁵

Inflammation is a second important indicator. TIMP-1 assays are not widely available in clinical practice. Of those assays commonly available in clinical laboratories, the most readily available are CRP and α 1-acid glycoprotein.

The PINI integrates CRP, α 1-acid glycoprotein, albumin, and prealbumin into a single score. We evaluated the PINI in patients entered in a clinical trial of two pressure relieving mattress products, which had identified no significant difference in the performance of the two products at preventing progression of grade 1 ulcers to more serious grade 3 ulcers.⁷ Additionally, we assayed RBP to investigate whether it would be more effective than albumin. This was substituted for albumin in the PINI formula. Results of the pressure ulcer prevention endpoint are reported elsewhere.⁷

Calculations used for indices are given in table 1.

METHODS

Subjects

The trial was ethically approved by the South East Staffordshire LREC. Patients were entered into the trial if

Abbreviations: BINI, Burton Inflammatory and Nutritional Index; CRP, C-reactive protein; PINI, Prognostic Inflammatory and Nutritional Index; RBP, retinol binding protein; TIMP, tissue inhibitor of matrix metalloproteinase

Calculation of indices

PINI = CRP (mg/l) $\times$ α 1-acid glycoprotein (mg/l)
 Albumin (g/l) $\times$ prealbumin (mg/l)
 BINI = CRP (mg/l) $\times$ α 1-acid glycoprotein (mg/l)*
 RBP (mg/l) $\times$ prealbumin (mg/l)*

*For the alternative calculation, retinal binding protein was substituted for albumin. This value was called the Burton Inflammatory and Nutritional Index (BINI).

they had a pressure ulcer grade 1 or above (European Pressure Ulcer Advisory Panel scale⁸) and were monitored to determine whether their ulcers worsened to grade 3 or above. In total, 158 patients were randomly assigned to either a Nimbus III alternating cell mattress (Huntleigh Healthcare Ltd, Luton, UK) or an RIK encapsulated fluid mattress (KCI Medical, Kidlington, Oxfordshire, UK). On admission, baseline Waterlow score, Burton score (a locally derived measure of nutritional status⁹), and ulcer severity were recorded after an informed consent procedure. Aliquots of serum from the admission were identified and frozen at -20°C for later analysis as a batch to minimise variance. In assessing mattress performance, overall clinical response, and pressure score responses (for all ulcers or the worst individual ulcer) were graded on a 3 point scale (worse, no change, improved).⁵

Analytical procedures

Albumin was analysed using a Beckman CX7 analyser with Beckman reagents (High Wycombe, UK). High sensitivity CRP and RBP were assayed by immunonephelometry using appropriate reagents (Dade-Behring, Milton Keynes, UK). Prealbumin and α 1-acid glycoprotein (orosomucoid), were assayed using a Cobas Mira analyser (Roche Diagnostic Systems, Welwyn, UK) and reagents from ABX Diagnostics (Sheffield, UK).

RESULTS

Baseline comparisons indicated that randomisation had been effective and that no subgroup was over-represented in either arm of the trial. No statistically significant difference between the performance of the mattresses was identified.⁷ The PINI is described as a prognostic indicator,¹ therefore, a sufficient length of stay for clinical progress to be assessed was essential. Serum samples were available for 105 patients for whom this criterion was met. As no difference between mattress types was identified, PINI/BINI results were evaluated against the clinical/pressure ulcer response without mattress type as a factor.

PINI/BINI results were regressed against Waterlow and Burton scores individually. No statistically significant relationship between the clinical scores and the PINI/BINI were identified.

Figure 1 ROC plot evaluating PINI as a predictive tool to identify whether patients' overall ulcer prognosis is bad.

The distribution of PINI and BINI scores was skewed and therefore results were log transformed. Table 2 shows the mean scores for each score according to whether the patients improved or worsened according to the three categories tested in the mattress trial. Both PINI and BINI showed statistically a significant difference between the means for the overall ulcer progress but the difference for BINI was less. Consequently, it would appear that PINI is a more effective marker, so further statistical analysis relates only to PINI. Because the dataset was small, and log transformation rarely completely normalises data, significance was also tested by a non-parametric Mann-Whitney test (overall ulcer worsening rank sum 1448, critical value 1430; non-significant).

Table 3 Overall ulcer progression according to PINI cutoff

PINI cutoff	Patients improving (n = 77)	Patients worsening (n = 24)
>5	56 (72.73%)	22 (91.67%)
>10	49 (63.64%)	20 (83.33%)
>25	34 (44.16%)	13 (54.17%)
>50	21 (27.27%)	10 (41.67%)
>100	12 (15.58%)	6 (25.00%)
>250	4 (5.19%)	2 (8.33%)

Table 2 Log PINI and BINI scores according to patient progress and clinical condition group

	Overall clinical progress	Overall ulcer progress	Progression of worst ulcer
Log ₁₀ (PINI)			
Worse	1.3031 (0.8811) (34)	1.5735 (0.6400) (24)	1.5715 (0.7010) (17)
No change	1.2740 (0.8462) (30)	1.7377 (0.6623) (4)	0.8647 (0.8364) (5)
Improved	1.1924 (0.8015) (41)	1.1543 (0.8720) (77)	1.2356 (0.8520) (83)
	SEM = 0.1962; z = 0.564; p = NS	SEM = 0.1641; z = 2.55; p = 0.011	SEM = 0.1940; z = 1.73; p = NS
Log ₁₀ (BINI)			
Worse	1.0921 (0.9623) (34)	1.4713 (0.6833) (24)	1.4546 (0.7371) (17)
No change	1.2341 (0.8583) (30)	0.7376 (1.4802) (4)	0.0455 (0.8262) (5)
Improved	1.0054 (0.9109) (41)	1.0947 (0.9338) (77)	1.1759 (0.9095) (83)
	SEM = 0.2179; z = 0.398; p = NS	SEM = 0.1754; z = 2.147; p = 0.032	SEM = 0.2047; z = 1.36; p = NS

Values shown are mean (SD) (n). Statistical significance was tested by evaluating the difference between the means for worse and improved, using the standard error of the mean. NS, non-significant.

The PINI was designed to be a prognostic indicator. Accordingly, a high value for PINI should indicate a worse prognosis. In the original publications, $\text{PINI} > 10$ was considered a significant value,^{1,2} but given the possibility of variation in standardisation between the assays used by those authors and by us, it was deemed appropriate to evaluate a range of possible cutoffs. Table 3 shows the patient outcome according to a range of PINI cutoffs, and fig 1 shows the same data as a ROC plot. The area under the curve (AUC) was calculated using ROC curve analysis software (accessed 3 June 2005; <http://espse.ed.psu.edu/spys/Watkins/Software/ROCanalysis.xls>), which gave the following results: $\text{AUC} = 0.6061$, $\text{SE}_{\text{AUC}} = 0.0684$, 95% confidence interval (CI) of the AUC 0.472 to 0.740. Using this standard error and testing against the line of identity gave $z = 1.5511$ and $p = 0.06$.

DISCUSSION

Pressure ulcers cause considerable patient morbidity and result in large costs for the health service. In 1997, it was estimated that the cost of pressure ulcers could be as high as £1 billion/annum.¹⁰ The Department of Health have also identified the prevalence of pressure ulcers as an indicator of the excellence of clinical care.¹¹ Despite this, there is surprisingly little evidence in the literature to allow choice of appropriate preventive measures,¹² and prediction tools remain rooted in a pragmatic clinical scoring system derived in the mid-1980s.³ As preventive equipment is expensive, it tends to be in short supply, and therefore an improved risk assessment tool could be extremely useful.

Previous work has demonstrated a relationship between PINI and TIMP-1, which was independent of the presence of pressure ulcers. However, PINI was originally designed to be a prognostic indicator and therefore the lack of relationship between PINI and presence of sores at baseline may not be surprising. Our results indicated that the PINI tends to be higher in those patients whose ulcers are likely to worsen. However, this can only be a tentative suggestion in need of further validation because, although PINI appeared to be a potential indicator of prognosis in respect of overall progress in pressure ulcer status owing to the positive parametric statistical assessment (table 1), the non-parametric assessment was negative, suggesting that it may not be effective. For the other categories (worst ulcer and general clinical progress), there was no significant difference for the means and therefore no predictive power. For the worst ulcer, this is not unexpected, as local factors (such as difficulty reducing pressure in particular areas) may be more important for a particular ulcer than for all ulcers suffered by the patient.

The ROC plot (fig 1) shows that there may be some predictive power derived from the PINI calculation. However, the difference between the line of identity and the ROC curve is small ($\text{AUC} = 0.6061$; 95% CI 0.472 to 0.740). As the CI for the ROC plot AUC included 0.5, which is equivalent to chance alone, and the z score indicated $p = 0.06$, we have to conclude that on the basis of this study, the PINI used alone is likely to be of limited clinical potential. It is possible, however, that in future it could be combined with other markers, perhaps

TAKE HOME MESSAGES

- Pressure ulcers cause considerable patient morbidity and result in large costs for the health service.
- Pressure relieving mattresses were evaluated using the Prognostic Inflammatory and Nutritional Index (PINI).
- There was a statistically significant difference in PINI values between patients whose pressure ulcers improved and those whose ulcers worsened in parametric testing, but not in non-parametric testing.
- The PINI appears to offer a potential route to improving pressure ulcer risk estimation and thus allocation of scarce equipment to improve prevention.

using a multivariate Gaussian approach akin to that used in Down's syndrome screening, to provide a more accurate prediction of those patients most likely to develop pressure ulcers, and therefore of those patients most in need of specialised preventative equipment/extra nursing attention. Further research to identify improved risk prediction methods is clearly indicated.

Authors' affiliations

A Stokes, Clinical Chemistry Department, Queen's Hospital, Burton-on-Trent, Staffordshire, UK

L Russell, Tissue Viability Department, Queen's Hospital, Burton-on-Trent, Staffordshire, UK

T M Reynolds, Clinical Chemistry Department, Queen's Hospital, Burton-on-Trent, Staffordshire, UK and Division of Sciences, Wolverhampton University, Wolverhampton, UK

REFERENCES

- 1 Perier C, Granouillet R, Chamson A, *et al*. Nutritional markers, acute phase reactants and tissue inhibitor of matrix metalloproteinase 1 in elderly patients with pressure sores. *Gerontology* 2002;**48**:298–301.
- 2 Ingenbleek Y, Carpentier YA. A prognostic inflammatory and nutritional index scoring critically ill patients. *Int J Vitam Nutr Res* 1985;**55**:91–101.
- 3 Waterlow J. Pressure sores: a risk assessment card. *Nurs Times* 1985;**81**:49–55.
- 4 Reynolds T. The future of nutrition and wound healing. *J Tiss Viab* 2001;**11**:5–12.
- 5 Velde MS. Nutritional assessment, therapy and monitoring. In: Burtis CA, Ashwood ER, eds. *Tietz textbook of clinical chemistry*, 3rd ed. Philadelphia: WB Saunders, 1999.
- 6 Fleck A, Raines G, Hawker F, *et al*. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985;**1**:781–4.
- 7 Russell L, Reynolds TM, Towns A, *et al*. Randomized comparison trial of RIK mattress and Huntleigh Nimbus 3. *Br J Nurs* 2003;**12**:254–9.
- 8 European Pressure Ulcer Advisory Panel Guidelines. A policy statement on prevention of pressure ulcers from the European Pressure Ulcer Advisory Panel. *Br J Nurs* 1998;**7**:888–90.
- 9 Russell L, Taylor J, Brewitt J, *et al*. Development and Validation of the Burton score: A tool for nutritional assessment. *J Tissue Viab* 1998;**8**:15–21.
- 10 Moody M. Fighting against pressure sores and a rise in legal suits. *Br J Health Manage* 1997;**3**:40–1.
- 11 DoH. *Pressure sores: a key quality indicator*. London: Health Publications Unit, 1993.
- 12 NICE. *Inherited clinical guidance B: pressure ulcer risk assessment and prevention*. London: NICE, 2001.