Critically ill patients frequently require inotropic and/or vasopressor support to treat circulatory shock. Subtypes of circulatory shock include hypovolaemic, cardiogenic, obstructive (e.g. pulmonary embolus, tension pneumothorax) and distributive (e.g. septic, neurogenic) shock. Patients with cardiogenic shock or a cardiogenic component to their shock state are frequently treated with dobutamine, an agent with positive inotropic effects and a mild net vasodilatory effect, an ‘inodilator’. Most other forms of shock are treated with noradrenaline or adrenaline. Both these agents have positive inotropic and vasoconstrictive effect ‘inopressors’. Noradrenaline is recommended as first-line therapy in septic shock. However, due to the limited availability of noradrenaline in South Africa, adrenaline is frequently used in lieu of the former. Clinical experience suggests that mortality in critically ill patients increases with increasing doses of inotropes and/or vasopressors. Critical care physicians are often faced with determining a threshold of inopressor support, above which rescue therapy is required or where survival is unlikely. The literature to help to determine the relevant threshold. A few studies have specifically explored the relationship between catecholamine dose and patient survival in critical care. Benbenishty et al. reported survival of only 4% in patients receiving >0.5 µg/kg/min of inotropic support. Jenkins et al. found that only 3.3% of patients receiving >100 µg/min of noradrenaline survived, Sviri et al. showed a mortality rate of 84% in patients receiving >40 µg/min of inotropic support, and Brown et al. reported a mortality rate of 83% in patients receiving ≥1 µg/kg/min. In contrast, Auchet et al. reported a survival rate of 39.6% in patients receiving >1 µg/kg/min, with Döpp-Zemel and Groeneveld noting a similar survival rate of 34.5% in patients receiving >20.9 µg/kg/min.

The disparate findings presented above make it difficult for physicians treating critically ill patients to take evidence-based decisions. This is further compounded by the abovementioned studies having been conducted in high-income countries, and it is unclear whether the results are applicable to low- and middle-income countries. Potential differences include those regarding drug availability (e.g. limited availability of noradrenaline in SA), ICU bed availability and triage and patient profile, including a young age and an increased incidence of HIV and sepsis in sub-Saharan Africa and SA specifically.

It is therefore important to evaluate the inotropic prescribing practices in the SA context, and to establish whether there is an association between dose and patient outcome. This will allow for improved evidence-based quality of care for critically ill SA patients.
Methods
This was a retrospective observational study of patients admitted to a multidisciplinary, closed, intensivist-run ICU in a tertiary academic hospital that serves the province of KwaZulu-Natal in SA.

All adult (≥18 years) patients requiring inotropic support with adrenaline or noradrenaline to maintain a mean arterial pressure >70 mmHg within the first 24 hours of ICU admission, were eligible for inclusion. The exclusion criteria were as follows: children (age <18 years), use of dobutamine, cardiogenic shock/refractory cardiac failure or documentation of a significant cardiogenic component in the setting of mixed forms of shock. Dobutamine use was excluded owing to lack of dose equivalency with the dominant catecholamines used in the study ICU, and owing to its drug-specific effects that prevent a direct pharmaceutical comparison between dobutamine and adrenaline/noradrenaline. Cardiogenic shock/refractory cardiac failure was an exclusion, as dobutamine is the catecholamine of choice in this condition. Data collection proceeded backwards from the date of ethical approval, with patients admitted from May 2016 to June 2018 included in the study.

Based on previous study data, using an alpha of 0.05, a power of 80% and an anticipated ratio of patients with high-dose/low-dose inotropic support of 0.2, a sample size of 112 was calculated.[19] It was unclear how appropriate the values used in the sample size calculation were for the study ICU (i.e. effect size and enrolment ratio) and it was therefore decided to use a sample size of 200 or include patients over a 2-year period, whichever came first. This would be logistically feasible, while allowing for a margin of safety, given the unknown factors discussed above.

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., USA) and MedCalc Statistical Software version 18.10.2 (MedCalc, Belgium). The categorical variables were described as percentages and compared using the χ² test or Fisher’s exact test, where appropriate. Continuous data were described using mean and standard deviation (SD) when normally distributed, and median and interquartile range (IQR) when the distribution was non-Gaussian. These data were compared using the independent samples t-test, Mann–Whitney U-test or Kruskal-Wallis test, respectively. Receiver operating characteristic (ROC) curves were constructed for inotrope dose and ICU mortality. The optimal cut-off point for each inotrope dose was determined by identifying the points on the curve closest to the (0,1) corner. These cut-off points were then combined with commonly considered clinical cut-off points, and the performance of each cut-off compared by determining the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR). Where appropriate, the area under the ROC curve (AUC) was compared using the method described by DeLong et al.[20]

Ethical approval
Ethical approval was granted by the University of KwaZulu-Natal Biomedical Research Ethics Committee (ref. no. BE052/18), the study hospital and the KwaZulu-Natal Department of Health (ref. no. HRKM099/18).

Results
The derivation of the study cohort is shown in Fig. 1. The final study population included 189 patients who required inotropic support with adrenaline and/or noradrenaline during the first 24 hours of ICU admission.

Table 1 shows the baseline demographic, organ dysfunction, outcome and inotrope data for the cohort, and provides univariate analyses between these variables and ICU mortality. Patients were not classified according to the ‘type’ of shock they exhibited, with those with suspected cardiogenic shock being excluded from the analysis; the included patients comprised mainly hypovolaemic/haemorrhagic shock and/or septic shock. In all cases, noradrenaline was the second inotrope.

The admission, 24-hour and maximum inotrope doses were all significantly higher in non-survivors than survivors (Table 1). Fig. 2 shows the ROC curve analyses for the abovementioned inotrope doses and ICU mortality. The AUC for the admission inotrope dose was 0.67 (95% confidence interval (CI) 0.59 - 0.76; p<0.001), for the 24-hour inotrope dose 0.76 (95% CI 0.69 - 0.84; p<0.001) and for the maximum inotrope dose within 24 hours 0.75 (95% CI 0.68 - 0.83). The AUC for the admission inotrope dose was significantly lower than for the 24-hour (p=0.042) and maximum (p=0.021) inotrope doses.

The ROC curves were used to select potential optimum cut-off points for inotrope doses; their performance and common clinical cut-off points are presented in Table 2. For a cut-off of 60 µg/min, the PPV for mortality approaches 90% for both admission and 24-hour inotropic requirements.

Table 3 shows the subgroup analyses for inotrope doses and ICU outcome according to the primary admission diagnosis. Median inotrope doses were significantly higher in non-survivors at all points and in all subgroups, except for trauma patients on admission.

Figs 3, 4 and 5 illustrate plots of inotrope doses and ICU outcomes by primary diagnosis. The maximum inotrope dose in survivors with non-communicable disease was 67 µg/min, 80 µg/min in sepsis and 143 µg/min in trauma.

Discussion
The ICU at which the study took place treats a notably young cohort of patients with a high incidence of trauma and infectious disease.[3] The cohort had a high severity of illness, as evidenced by the admission SOFA score, and consequently a high mortality rate. The study included a heterogeneous group of medical, surgical and obstetric patients with a spectrum of infectious, traumatic and non-communicable primary pathological conditions. Patients were not classified according to type of shock due to the many contributing factors to shock in any patient; however, if a significant cardiogenic component was known or suspected, such patients were excluded.

Table 1: Baseline demographics, organ dysfunction, outcome and inotrope data for the cohort

| Age: <18 years | n=12 |
| Dobutamine use | n=14 |
| Transferred to another ICU (no outcome available) | n=2 |

Table 2: ROC curve analyses for admission inotrope dose and ICU mortality

| Area Under the Curve (AUC) | p-value |
|---------------------------|---------|
| Admission inotrope dose   | 0.67    |
| 24-hour inotrope dose     | 0.76    |
| Maximum inotrope dose     | 0.75    |

Table 3: Subgroup analyses for inotrope doses and ICU outcome

| Age: <18 years | n=12 |
| Survived      | n=96 (50.8%) |
| Died          | n=93 (49.2%) |

Fig. 1: Derivation of study cohort. (ICU = intensive care unit.)
The dominant inotrope used was adrenaline, with noradrenaline being used in a small subset of patients, which reflects its limited availability in SA. It was expected that for patients with a poor prognosis, the treating intensivist may have limited the maximum inotrope dose, which would have introduced bias into the study. However, there were written instructions to limit inotropic support for only 3 patients during the first 24 hours of admission, and all survived to ICU discharge. This possibly reflects a reluctance among the treating physicians to limit inotropic support early in the course of critical illness until a trial period of active haemodynamic optimisation has been completed.

Table 1. Summary data for cohort and univariate analyses for ICU outcome

| Variable                             | Characteristics | Total, median (IQR)* | Survived (n=96), median (IQR)* | Died (n=93), median (IQR)* | p-value |
|--------------------------------------|-----------------|----------------------|--------------------------------|---------------------------|---------|
| Age, years                           |                 | 40                   | 35                             | 44                        | 0.006   |
|                                      |                 | (28.0 - 59.0)        | (27.0 - 53.0)                  | (32.0 - 63.0)             |         |
| Female, n (%)                        |                 | 95 (50.3)            | 47 (49.0)                      | 48 (51.6)                 | 0.715   |
| Admission discipline, n (%)          | O&G             | 19 (10.1)            | 12 (12.5)                      | 7 (7.5)                   | 0.519   |
|                                      | Medical         | 76 (40.2)            | 38 (39.6)                      | 38 (40.9)                 |         |
|                                      | Surgical        | 94 (49.7)            | 46 (47.9)                      | 48 (51.6)                 |         |
| Primary diagnosis, n (%)             | Sepsis          | 68 (36.0)            | 28 (29.2)                      | 40 (40.0)                 | 0.088   |
|                                      | Trauma          | 47 (24.9)            | 29 (30.2)                      | 18 (19.4)                 |         |
|                                      | Non-communicable| 74 (39.2)            | 39 (40.6)                      | 35 (37.6)                 |         |
| Postoperative, n (%)                 |                 | 103 (54.5)           | 56 (58.3)                      | 47 (50.5)                 | 0.282   |
| Mechanical ventilation (1st 24 hours), n (%) |                 | 189 (100)           | 96 (100)                       | 93 (100)                  |         |
| RRT (1st 24 hours), n (%)            |                 | 16 (8.5)             | 6 (6.3)                        | 10 (10.8)                 | 0.266   |
| Death within 24 hours, n (%)         |                 | 20 (10.6)            | 0 (0)                          | 20 (21.5)                 | <0.001  |
| Discharge within 24 hours, n (%)     |                 | 1 (0.5)              | 1 (1.0)                        | 0 (0)                     | 0.324   |
| ICU LOS                              |                 | 4.0 (2.0 - 6.0)      | 4.0 (3.0 - 7.0)                | 3.0 (1.0 - 5.0)           | <0.001  |
| SOFA score on admission              |                 | 11                   | 11.0                           | 12.0                      | <0.001  |
|                                      |                 | (10.0 - 13.0)        | (10.0 - 13.0)                  | (10.0 - 14.0)             |         |
| SOFA score at 24 hours               |                 | 12.0                 | 11.0                           | 13.0                      | <0.001  |
|                                      |                 | (10.0 - 13.0)        | (9.0 - 12.0)                   | (11.0 - 14.0)             |         |
| AKI within first 24 hours, n (%)     |                 | 77 (41.0)            | 31 (32.3)                      | 46 (50.0)                 | 0.014   |
| Inotrope 1 on admission, n (%)       | Adrenaline      | 184 (97.4)           | 93 (96.9)                      | 91 (97.8)                 | 0.857   |
|                                      | Noradrenaline   | 2 (1.1)              | 1 (1.0)                        | 1 (1.1)                   |         |
|                                      | Nil             | 3 (1.6)              | 2 (2.1)                        | 1 (1.1)                   |         |
| Use of second inotrope on admission, n (%) |                 | 10 (5.3)            | 0 (0)                          | 10 (10.8)                 | 0.001   |
| Inotrope 1 at 24 hours, n (%)        | Adrenaline      | 148 (88.1)           | 80 (84.2)                      | 68 (93.2)                 | 0.062   |
|                                      | Noradrenaline   | 1 (0.6)              | 0 (0)                          | 1 (1.4)                   |         |
|                                      | Nil             | 19 (11.1)            | 15 (15.8)                      | 4 (5.5)                   |         |
| Use of second inotrope at 24 hours, n (%) |                 | 10 (6.0)            | 2 (2.1)                        | 8 (11.0)                  | 0.016   |
| Total admission inotrope dose, µg/min|                 | 20.0                 | 13.3                           | 26.7                      | <0.001  |
|                                      |                 | (13.3 - 40.0)        | (6.7 - 26.7)                   | (13.3 - 60.0)             |         |
| Total 24-hour inotrope dose, µg/min   |                 | 13.3                 | 6.7                            | 34.7                      | <0.001  |
|                                      |                 | (4.0 - 40.0)         | (2.7 - 16.0)                   | (10.7 - 66.7)             |         |
| Maximum inotrope dose in first 24 hours, µg/min |               | 40.0                 | 26.7                           | 66.7                      | <0.001  |
|                                      |                 | (20.0 - 66.7)        | (13.3 - 40.0)                  | (30.7 - 93.3)             |         |
| Non-escalation or withdrawal of inotropic support during first 24 hours, n (%) | | 3 (1.6)                | 3 (3.1)                         | 0 (0)                     | 0.086   |

ICU = intensive care unit; IQR = interquartile range; O&G = obstetrics and gynaecology; RRT = renal replacement therapy; LOS = length of stay; SOFA = Sequential Organ Failure Assessment; AKI = acute kidney injury.

*Except where otherwise indicated.

1.0
Sensitivity
0.8
0.6
0.4
0.2
0.0
0               0.2              0.4              0.6              0.8             1.0
Speci/ficity
24-hour inotrope dose, µg/min
Maximum inotrope dose, µg/min
Total 24-hour inotrope dose, µg/min
Admission inotrope dose, µg/min
Reference line

Fig. 2. Receiver operating characteristic curve for inotrope dose and intensive care unit mortality.

from the study. The dominant inotrope used was adrenaline, with noradrenaline being used in a small subset of patients, which reflects its limited availability in SA. It was expected that for patients with a poor prognosis, the treating intensivist may have limited the maximum inotrope dose, which would have introduced bias into the study. However, there were written instructions to limit inotropic support for only 3 patients during the first 24 hours of admission, and all survived to ICU discharge. This possibly reflects a reluctance among the treating physicians to limit inotropic support early in the course of critical illness until a trial period of active haemodynamic optimisation has been completed.
Table 2. Inotropic cut-off analyses for ICU mortality*  

| Timing of inotropic support | Inotrope dose cut-off, µg/min | Sensitivity, % | Specificity, % | NPV, % | PPV, % | PLR | NLR |
|-----------------------------|-------------------------------|----------------|----------------|--------|--------|-----|-----|
| Admission                   | 7                             | 88.2           | 27.1           | 70.3   | 53.9   | 1.21| 0.44|
|                             | 13                            | 84.9           | 33.3           | 69.6   | 55.2   | 1.27| 0.45|
|                             | 21                            | 62.4           | 62.5           | 63.2   | 61.7   | 1.66| 0.60|
|                             | 25                            | 60.2           | 69.8           | 64.4   | 65.9   | 1.99| 0.57|
|                             | 40                            | 38.7           | 86.5           | 59.3   | 73.5   | 2.86| 0.71|
|                             | 47                            | 31.2           | 93.8           | 58.4   | 82.9   | 4.99| 0.73|
|                             | 60                            | 25.8           | 96.9           | 57.4   | 88.9   | 8.26| 0.77|
|                             | 80                            | 10.8           | 99.0           | 53.4   | 90.9   | 10.32| 0.90|
|                             | 100                           | 6.5            | 100            | 52.5   | 100    | 1.94| 0.94|
| 24 hours                    | 7                             | 83.6           | 53.2           | 80.6   | 58.1   | 1.79| 0.31|
|                             | 13                            | 72.6           | 62.8           | 74.7   | 60.2   | 1.95| 0.44|
|                             | 21                            | 65.8           | 79.8           | 75.0   | 71.6   | 3.25| 0.40|
|                             | 25                            | 58.9           | 83.0           | 72.2   | 72.9   | 3.46| 0.50|
|                             | 40                            | 47.9           | 92.6           | 69.6   | 83.3   | 4.44| 0.56|
|                             | 47                            | 38.4           | 93.6           | 66.2   | 82.4   | 6.01| 0.66|
|                             | 60                            | 34.2           | 96.0           | 65.5   | 89.3   | 10.73| 0.68|
|                             | 80                            | 21.9           | 97.9           | 61.7   | 88.9   | 10.30| 0.80|
|                             | 100                           | 15.1           | 98.9           | 60.0   | 91.7   | 14.16| 0.86|
| Maximum                     | 7                             | 96.8           | 10.4           | 76.9   | 51.1   | 1.08| 0.31|
|                             | 13                            | 94.6           | 19.8           | 79.2   | 53.3   | 1.18| 0.27|
|                             | 21                            | 83.9           | 44.8           | 74.1   | 59.5   | 1.52| 0.36|
|                             | 25                            | 81.7           | 49.0           | 73.4   | 60.8   | 1.60| 0.37|
|                             | 40                            | 71.0           | 69.8           | 71.3   | 69.5   | 2.35| 0.42|
|                             | 47                            | 64.5           | 80.2           | 70.0   | 75.9   | 3.26| 0.44|
|                             | 60                            | 53.8           | 89.6           | 66.7   | 83.3   | 5.16| 0.52|
|                             | 80                            | 32.3           | 95.8%          | 59.4   | 88.2   | 7.74| 0.71|
|                             | 100                           | 21.5           | 97.9           | 56.3   | 90.9   | 10.32| 0.80|

ICU = intensive care unit; NPV = negative predictive value; PPV = positive predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio.

Table 3. Comparison of median inotrope dose according to primary diagnosis and ICU outcome  

| Inotrope dose, µg/min | Primary diagnosis | Survived, median (IQR) | p-value* | Died, median (IQR) | p-value* | p-value† |
|-----------------------|------------------|------------------------|----------|-------------------|----------|----------|
| Admission             | Sepsis           | 13.3 (6.7 - 26.7)      | 0.645    | 26.7 (16.7 - 61.7) | 0.855    | 0.001    |
|                       | Trauma           | 16.0 (10.7 - 26.7)     |          | 25.0 (13.3 - 66.7) |          | 0.135    |
|                       | Non-communicable | 16.0 (6.7 - 26.7)      |          | 26.7 (13.3 - 53.3) |          | 0.004    |
| 24 hours              | Sepsis           | 5.3 (2.7 - 11.3)       | 0.475    | 21.3 (8.0 - 73.3)  | 0.066    | 0.001    |
|                       | Trauma           | 10.7 (2.7 - 20.0)      |          | 66.7 (50.7 - 93.3) | <0.001   |          |
|                       | Non-communicable | 6.7 (1.3 - 18.7)       |          | 33.3 (13.3 - 60.0) | <0.001   |          |
| Maximum               | Sepsis           | 19.3 (11.3 - 26.7)     | 0.166    | 66.7 (24.0 - 105.0)| 0.248    | <0.001   |
|                       | Trauma           | 26.7 (13.3 - 40.0)     |          | 73.3 (50.7 - 93.3) | 0.001    |          |
|                       | Non-communicable | 26.7 (16.0 - 48.0)     |          | 53.3 (26.7 - 66.7) | <0.001   |          |

ICU = intensive care unit; IQR = interquartile range.

*Comparing median inotrope dose between sepsis, trauma and non-communicable diagnoses (Kruskal-Wallis test).
†Comparing median inotrope dose between survivors and non-survivors (Mann-Whitney U-test).
There was a statistically significant difference in the median inotrope dose between survivors and non-survivors for admission, 24-hour and maximum inotrope doses, which was an anticipated finding. The magnitude of the difference appeared more marked for 24-hour and maximum inotrope doses than for admission inotrope dose. Similarly, ROC curve analyses showed that inotrope dose was significantly associated with ICU mortality, with reasonable predictive accuracy. The performance of 24-hour and maximum inotrope doses was significantly better than for the admission inotrope dose.

While statistically significant, these findings do not necessarily provide the practising clinician with clinically relevant data. To this end, the performance of various inotropic cut-off points was evaluated (see Methods above) (Table 2). The NPV of low doses of inotropic support (<13 µg/min) is reasonably high (≥70%), indicating that these patients are likely to survive ICU admission. This is particularly true if the inotrope dose remains low, with an NPV of 80.6% if inotropic support at 24 hours is <7 µg/min. However, the main clinical challenge for intensive care physicians is predicting which patients are unlikely to survive ICU stay. This is especially relevant in resource-limited settings, due to the scarcity and cost of critical care. In this regard, the PPV for ICU mortality of inotropic support approaches 90% for both admission and 24-hour inotrope doses, with similar findings for a maximum inotrope dose ≥80 µg/min. Similarly, the specificity for an admission or 24-hour cut-off of 60 µg/min is 96.9% and 96.8%, respectively, implying a very low false-positive rate for ICU mortality.

With a mortality rate approaching 90% for an admission or 24-hour inotrope dose ≥60 µg/min, the clinical and ethical question that needs to be considered is whether this is an appropriate ceiling for inotropic support. A clear maximum recommended dose of inotropic support would allow clinicians to triage patients on admission, or at least at 24 hours after admission. This would reduce patient exposure to unnecessary artificial life-sustaining therapy and reduce inappropriate utilisation of critical care resources. The value judgement to be made is whether 90% mortality provides adequate clinical certainty. For many clinicians, this would not be adequate certainty, with a single inotrope dose therefore being unlikely to replace clinical judgement. A counter argument is that a strong case would need to be made by a treating physician who wishes
to continue with >60 µg/min of inotropic support. With only a 10% chance of survival, it could be argued that ongoing artificial life-sustaining therapy is not ethically appropriate.

Direct comparisons with other studies in the field are difficult owing to differences in patient population and study methodology. The findings of this study are, however, broadly compatible with those of Benbenishty et al., Jenkins et al., Sviri et al. and Brown et al., but show higher mortality than those of Auchet et al. and Döpp-Zemel and Groeneveld. These findings highlight the difficulties of applying studies from other settings to a specific clinical population and illustrate the importance of conducting locally relevant research.

Subgroup analysis suggests clinically relevant differences in response to inotropic support according to the primary pathology. While no survivors were noted who had been administered inotropic doses >80 µg/min in sepsis and non-communicable disease, survival up to the maximum inotrope dose of 143 µg/min was seen in trauma. This is most likely due to trauma patients being younger and having fewer comorbidities, and most importantly, having a readily reversible underlying pathology. These subgroup differences should be considered the limitation of inotropic support, while more liberal use of higher thresholds in trauma patients is recommended.

Study strengths and limitations
This study has numerous strengths, most notably that it is the first such study in a resource-limited setting and in sub-Saharan Africa. It also explored early inotrope dose, the use of clinically relevant cut-off points to improve its clinical utility and potentially clinically relevant subgroup differences.

The study limitations include the retrospective nature and relatively small population size. The classification of the patient’s shock state was particularly difficult from retrospective notes and, therefore, other than excluding patients with an apparent cardiogenic component, further categorisation of the shock state was not used. The single-centre nature of the study also limits the generalisability of the results. For this reason, a larger prospective multicentre study exploring these issues is strongly advised. The other factor that may have introduced bias into the study is the limitation of inotrope dose by the treating physician. While this was noted in only 3 patients (all of whom survived their ICU admission) due to the retrospective nature of the study, the limitations of inotropic support may have occurred, but were not documented in the clinical notes. The kinetics of inotropic support were not evaluated, and some factors, such as duration of peak inotropic support and changes in inotropic support, may have significant prognostic implications and warrant further investigation.

Conclusions
The study found early inotropic dose to be significantly associated with ICU mortality. There was also a statistically significant difference in median inotropic dose between survivors and non-survivors for admission, 24-hour and maximum inotrope doses. Low doses of inotropic support (<13 µg/min) are associated with high ICU survival (≥70%), while high doses of inotropic support (≥ 60 µg/min) are associated with a mortality approaching 90% for both admission and 24-hour inotrope doses, with similar findings for a maximum inotrope dose ≥80 µg/min. These findings suggest that early inotrope dose may be useful in ICU risk prediction. The results also suggest that high doses of inotropic support in patients with sepsis and non-communicable disease are unlikely to be beneficial, but more appropriate in the acute phase of trauma. Given the high volume of young patients who require ICU support in SA, further studies to validate these findings are recommended.

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