

Picterus® Jaundice Pro as a screening tool for neonatal jaundice

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Contents:

1. Summary
2. Background
3. Method
4. Results
 - 4.1 Demographics
 - 4.2 Correlation studies
 - 4.3 Agreement studies
 - 4.4 The impact of skin pigmentation on the precision of Picterus JP Jaundice pro measurements
 - 4.5 Picterus JP Jaundice Pro as a screening device
5. Conclusions
7. References
8. Appendix

1. Summary

Raised serum bilirubin concentration is common in the neonatal period and can cause jaundice (yellow discolouration of the skin). High levels of bilirubin, though, can injure the developing brain. Effective treatments to reduce bilirubin levels and treatment thresholds for these treatments are well defined. Blood sampling to measure total serum bilirubin (TSB) is the commonest test performed in babies during the neonatal period. A reliable non-invasive method of jaundice assessment would be welcomed by clinicians.

Transcutaneous bilirubinometry (TcB) is recommended for the screening of babies to determine whether or not they require TSB. Picterus Jaundice Pro (JP) measures bilirubin concentrations from colour analysis of images of a baby's skin acquired with a smart phone camera. The advantages of this system compared to TcB are the lower cost and ease of deployment.

The aim of this paper is to study how well Picterus JP measures neonatal TSB.

Data have been collected from 8 separate evaluation studies in different parts of the world. In these studies, 790 neonates with a gestation of 35 weeks or more who were more than 24 hours old had paired measurements of bilirubin by Picturus JP and TSB. Babies recruited included those who were having blood taken for TSB and those having blood taken for other clinical, non-jaundice related, reasons.

There was a significant correlation between the 2 methods ($n = 790$, $r = 0.78$, $p < 0.0001$). The relationship was much stronger in babies with TSB in the zone $< 300 \mu\text{mol/L}$ ($n = 735$, $r = 0.74$, $p < 0.001$) than in those with TSB in the zone $> 300 \mu\text{mol/L}$ ($n = 55$, $r = 0.32$, $p = 0.018$). The nature of the relationship was also different in these 2 zones, with an increase in the Picturus JP values of $0.85 \mu\text{mol/L}$ for every $1 \mu\text{mol/L}$ increase in TSB when TSB was $< 300 \mu\text{mol/L}$ but only $0.17 \mu\text{mol/L}$ for every $1 \mu\text{mol/L}$ increase when TSB was above $300 \mu\text{mol/L}$.

Agreement between the two methods was assessed by the method of Bland and Altman. The mean difference between the 2 results (Picturus-TSB) was $9.39 \mu\text{mol/L}$, but there was significant scatter in differences from different measurement pairs, so that the 95% limits of agreement were $-95.3 \mu\text{mol/L}$ and $114.11 \mu\text{mol/L}$. Agreement was better than this when TSB was $< 300 \mu\text{mol/L}$ (mean difference is $14.86 \mu\text{mol/L}$, the 95% limits of agreement are between $-81.7 \mu\text{mol/L}$ and $110.59 \mu\text{mol/L}$). The agreement for measurements when TSB was above $300 \mu\text{mol/L}$ was very poor (the mean difference is $-63.6 \mu\text{mol/L}$, the 95% limits of agreement are between $-177.9 \mu\text{mol/L}$ and $50.7 \mu\text{mol/L}$).

There are concerns that TcB may be less accurate in babies with darker skin pigmentation. The Picturus JP system has allowed study of this by comparing the difference between Picturus JP measurement and TSB with the 'red-channel' of the image obtained by the system. The red channel is a surrogate marker of the degree of skin pigmentation. There was a weak, but statistically significant correlation between the difference in measurement values and the red channel ($n = 786$, $r = -0.13$, $p = 0.0003$). This suggests that the Picturus JP value more likely to overestimate TSB in darker skinned babies. Regression analysis suggests that only 1.7% of the variability in the differences can be explained by skin pigmentation and that the magnitude of any increased error seen is relatively small in relation to the overall degree of imprecision. The relationship between skin colour and Picturus JP precision is felt to be of no clinical consequence.

Like TcB, Picturus JP cannot be used to measure TSB accurately. This is particularly the case at levels of TcB when neurological injury becomes possible. Picturus JP is licensed for neonatal jaundice screening. Using the system to identify which jaundiced babies require TSB would be helpful as it could reduce TSB measurements and reduce hospital visits etc.

Receiver Operator Characteristic (ROC) curves were constructed. The area under the ROC to detect a TSB of $> 250 \mu\text{mol/L}$ was 0.93. A Picturus JP measurement of $151.2 \mu\text{mol/L}$ gives 100% sensitivity and 58.7% specificity for detection of TSB $> 250 \mu\text{mol/L}$. The area under the ROC to detect a TSB of $> 300 \mu\text{mol/L}$ was 0.94. A Picturus JP measurement of $193 \mu\text{mol/L}$ gives 100% sensitivity and 71% specificity for detection of TSB $> 250 \mu\text{mol/L}$.

A series of ROC curves were constructed to detect the phototherapy thresholds at the end of each 24 hours in babies from 35 to 38+ weeks gestation using the National Institute for Clinical Excellence (NICE) phototherapy threshold charts. Using the Picturus value from these curves that gave 100% sensitivity, a series of "Picturus charts" were produced to identify the levels of Picturus JP that would show that a TSB measurement was required. If these charts had been

applied to the population on which they had been developed (the subjects in this study) then the need for phototherapy would have been identified with 100% sensitivity and specificity of 38.4%. 267 babies (33.8% of the total) would have avoided a blood test. This is likely to be an overestimate though as some of the babies recruited did not have jaundice and would not have had a TSB measured anyway other than for the purposes of this study.

NICE guidelines state that if a baby born at 38 weeks or more has a TSB below but within 50 $\mu\text{mol/L}$ of the phototherapy line, then they should have another TSB measurement 18 or 24 hours later, depending on the presence or absence of risk factors. Using the same approach as above a series of Picturus charts were developed to identify babies who required phototherapy or a repeat TSB. Using these, detection of babies who required phototherapy or repeat TSB was achieved with a sensitivity of 96.4% and a specificity of 24.8%. This would have prevented 155 of the 790 blood tests (19.6%), although this may be an overestimate of what would be seen in a population of babies who were having blood tests for jaundice assessment only, as above.

Picturus JP appears to be a viable alternative for use as a screening method to identify babies who require TSB. It is unsurprising that the method developed in this study should show 100% sensitivity as the Picturus JP thresholds were chosen at the 100% sensitivity level. The system should be evaluated in a separate validation study to ensure that the system is accurate in another population of babies. This validation cohort should only include babies who are having their jaundice assessed, so that a better estimate of the reduction in blood tests can be made.

2. Background

Unconjugated serum bilirubin levels are raised in the early neonatal period compared to other times of life. This causes jaundice, a yellow discolouration of the skin and/or sclera. For the vast majority of babies this is part of the normal physiological neonatal transition. The unconjugated bilirubin molecule can cross the blood brain barrier, however, and very high levels of bilirubin are neurotoxic, causing a bilirubin encephalopathy (Kernicterus) with high levels of mortality and neurological disability in survivors. There are effective treatments that reduce bilirubin levels and protect the brains of babies with pathologically elevated bilirubin levels (phototherapy and exchange blood transfusion). A challenge to clinicians working in neonatal care is to differentiate between harmless physiological jaundice and potentially brain threatening jaundice which requires intervention.

Identification of jaundice that requires treatment by visual inspection has been shown to be unreliable (1). The gold standard test is a measurement of the total serum bilirubin in a blood test (TSB). Because of the unreliability of visual inspection and the serious consequences of failing to recognise and treat very high bilirubin levels, most clinicians adopt a risk averse policy of performing TSB very readily. TSB is the most commonly performed blood test in the neonatal period and the vast majority of measurements are below the levels requiring treatment.

Performing TSB is painful for the baby and expensive. It can also be disruptive for the family and clinical services. Most cases of jaundice will become apparent after 48 hours, when the majority of babies are at home. Babies typically have to return to hospital for a TSB to be performed, even though most of these TSB tests will not require intervention.

A rapid, non-invasive, method of measuring bilirubin levels has the potential to benefit families. Transcutaneous Bilirubinometry (TcB) is a widely accepted non-invasive method of assessing

neonatal jaundice. It measures the intensity of light reflected from the baby's skin and measures bilirubin concentration from the known absorption spectrum of the bilirubin molecule. It has been shown to lack the precision required to make decisions about treatment, but is recommended to be used as a screening tool to assist clinicians in identifying which babies may need a TSB (2, 3).

Picterus Jaundice Pro (Picterus JP) is an alternative non-invasive rapid method of assessing neonatal jaundice. It is approved for use by both parents and healthcare professionals. The device uses a smartphone app and a Picterus® Calibration Card to estimate bilirubin levels from images of the skin of a newborn's chest (Figure 1). The Picterus® Calibration Card adjusts for different light conditions and camera sensors. The advantages of this system compared to TcB are the ease of deployment (no extra equipment is required other than the smartphone that most clinicians will already have, it self-calibrates, and there is a lower cost of the service).



Figure 1 – The Picterus® Calibration card is placed on the skin of the newborn's chest. The app automatically takes pictures when the card is detected. An image quality check and bilirubin calculation is performed and the result is displayed within seconds. For more information, please refer to the Picterus website (<https://picterus.com/>).

The aim of this investigation has been to evaluate the precision of the Picterus JP system in measuring jaundice in the newborn and to assess its potential role as a screening device. The evaluation has been performed on data collected from eight separate studies performed at different settings across the globe. All of the studies followed a similar design, and all were approved by the relevant local research ethics approval body. Written informed consent was collected for all subjects. Some of these studies have already been reported separately (4).

In addition, several other validation studies have been published using previous versions of the system. A summary of these publications and details of which version of the analysis software they used can be found at <https://picterus.com/clinical-evidence/>

3. Methods

The details of the included studies are shown in Table 1.

Study site	Data collection period	subjects (n)
Intermountain Medical Center, McKay-Dee Hospital, and Utah, Valley Hospital, USA	February - July, 2024	199
University of Chicago, USA	March - October, 2024	72
Hospital General Zona 1 Oaxaca, Mexico	February 2023-June 2024	144
Candida Vargas Institute, Brazil	January - March, 2025	155
Gulu University & Teaching Hospitals, Uganda	February - April, 2025	102
University Children's Hospital in Skopje, North Macedonia	April - October, 2025	27
Multicentre, India	July - October, 2025	60
Imperial College London, UK	November - December, 2025	31
Total		790

Table 1. Location of study sites.

Each subject included in these studies had a jaundice measurement made by the Picterus JP system and a TSB made at the same time. Both procedures were performed within a time span of 60 minutes.

Newborns included met the following criteria: age between 1 to 14 days, gestational age of at least 35 weeks, birth weight of 2000 g or more, not previously received phototherapy and requiring a blood sample either for clinically suspected jaundice or as part of clinical routine practice. Newborns were excluded if they had a condition or treatment that affected skin colour or appearance, other than jaundice. Infants receiving or previously receiving phototherapy were also excluded. Each subject has contributed only one pair of measurements to the data set used in this analysis.

TSB levels were measured with a blood sample obtained by either heel prick or venous puncture. Samples were immediately processed at the hospitals' laboratory by trained personnel. Different TSB analytical methods were used across study sites, depending on local availability and routine laboratory practice.

To perform a Picterus JP scan, the Picterus® Calibration Card was placed on a flat part of the newborn's chest and an image set, consisting of 3 images with and 3 without flash, was automatically captured on a smartphone using the Picterus JP app.

4. Results

4.1 Demographics

Although the protocol specified that babies should be over 24 hours of age, 22 subjects were recruited between 21.7 and 23.9 hours. These babies have been included in this analysis. The demographics of the subjects is shown in Table 2.

	Median	Min	Max
Birthweight (g)	3160	2000	5700
Gestation (completed weeks)	39	35	43
Age at time of study (hours)	45.7	21.7	319
TSB ($\mu\text{mol/L}$)	145.4	8.38	570.8
TSB (mg/dL)	8.5	0.5	33.4
Picterus JP ($\mu\text{mol/L}$)	149.1	38.6	362
Picterus JP (Mg/dL)	8.7	2.3	21.2

Table 2. Demographic description of study cohort.

The inclusion of newborns from sites spanning multiple continents with diverse populations ensured representation of all skin tones within the study cohort. This is important, since transcutaneous bilirubin assessments are affected by the presence of melanin (3, 5,6, 7). For each newborn, a calibrated red-channel (R-channel) value was determined from Picterus JP images. The R-channel value is affected by the melanin content of a newborn's skin. The R-channel values in this data set range from 0.14 to 0.56; lower values indicate darker skin. Examples of newborn skin tones for R-channel values are shown (Figure 2). The impact of skin pigmentation on the precision of Picterus JP measurements is presented later in this report.

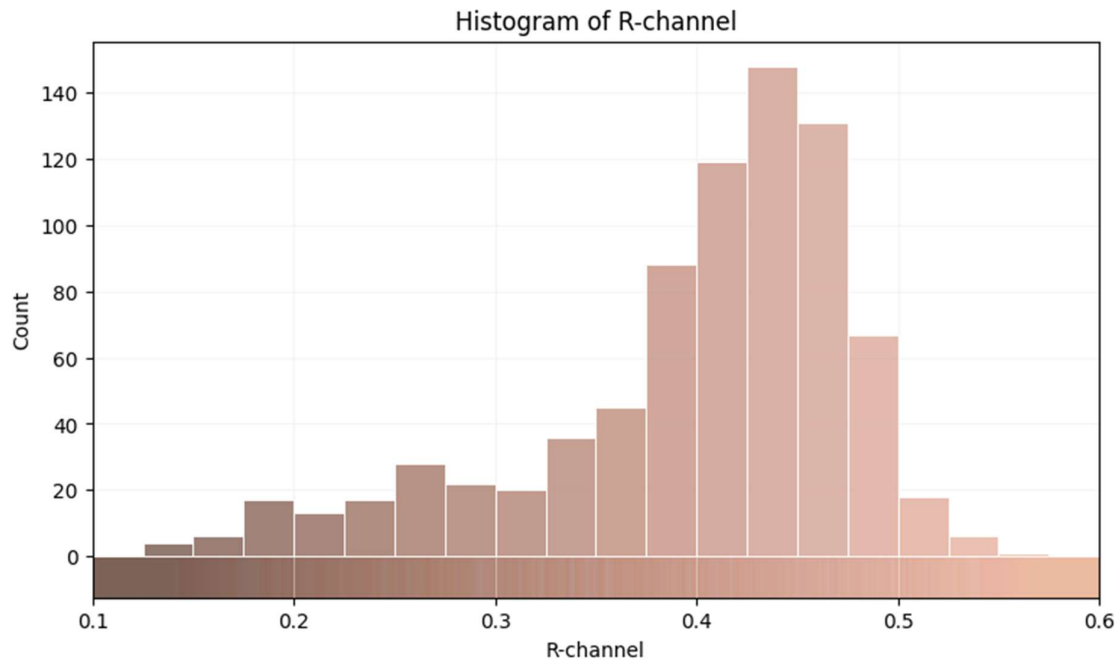


Figure 2. The R-channel values (x-axis) from Picterus® Jaundice Pro skin images were used as a proxy for newborn skin tone. Each histogram bar represents the number of samples within an R-channel bin. The bar colours and the gradient bar indicate the mean skin colour of the samples in the corresponding R-channel range.

4.2 Correlation analysis

Correlation between Picterus JP values and TSB were assessed using Pearson's correlation coefficient. The relationship between Picterus JP and TSB was described using simple linear regression.

There is a statistically significant positive correlation between Picterus JP measurements and TSB ($n = 790$, $r = 0.78$, $p < 0.001$). The equation of the regression line is $\text{Picterus JP} = 52.65 + 0.74 \times \text{TSB}$. The relationship is shown in Figure 3.

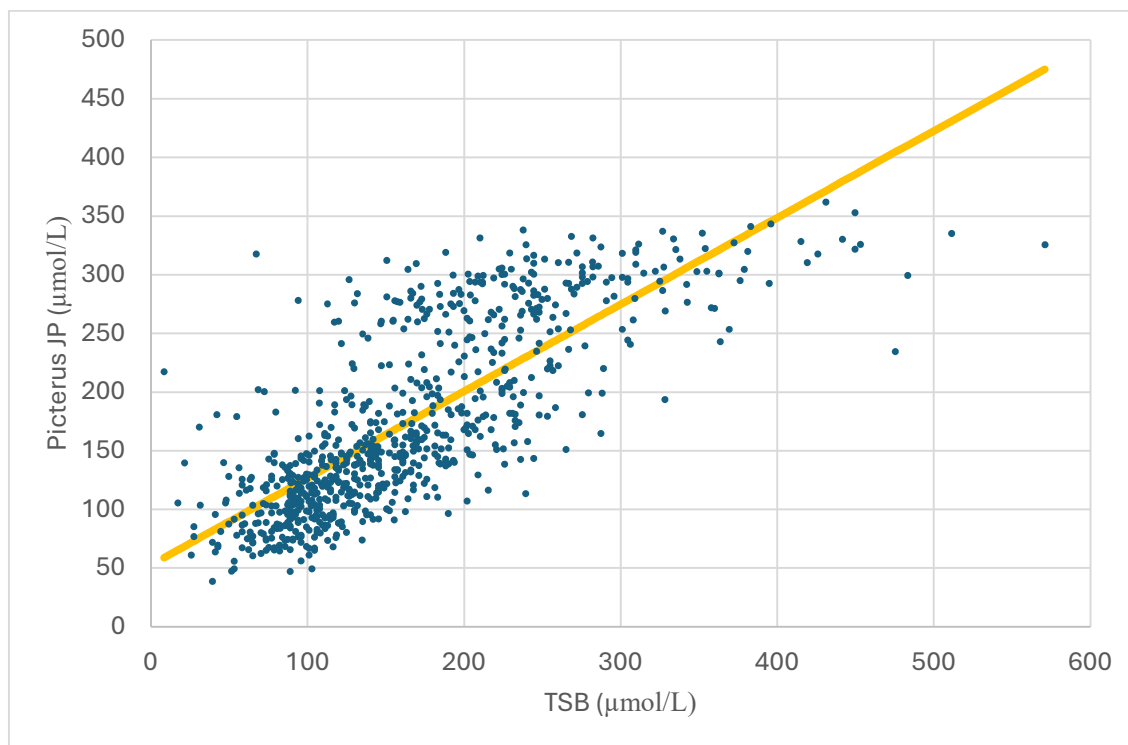


Figure 3. Picterus JP plotted against corresponding TSB values. The line shows the regression equation ($\text{Picterus JP} = 52.65 + 0.74 \times \text{TSB}$).

Visual inspection of the plotted data shows that there is considerable scatter around the regression line and that there appears to be a biphasic relationship between the two measurements, with a different relationship seen when TSB is below 300 $\mu\text{mol/L}$ to that seen when TSB is above 300 $\mu\text{mol/L}$.

For measurement pairs with a TSB below 300 $\mu\text{mol/L}$ there is a statistically significant strong positive correlation ($n = 735$, $r = 0.74$, $p < 0.001$). For each 1 $\mu\text{mol/L}$ increase in TSB, there is a corresponding 0.86 $\mu\text{mol/L}$ increase in the Picterus JP measurement ($\text{Picterus JP} = 35.63 + 0.86 \times \text{TSB}$). R squared for this regression is 0.55, showing that 55% of the variability in Picterus JP values can be explained by variation in the TSB measurements.

For measurement pairs with a TSB above 300 $\mu\text{mol/L}$ there is also a statistically significant, but much weaker, positive correlation ($n = 55$, $r = 0.32$, $p = 0.018$). The regression equation shows a much shallower slope, with only modest increases in Picterus JP value with each increase in TSB ($\text{Picterus JP} = 237.89 + (0.17 \times \text{TSB})$). R squared for this regression is only 0.1, showing that only 10% of the variability in Picterus JP values in this range can be attributed to variability in TSB.

These relationships are shown in Figure 4.

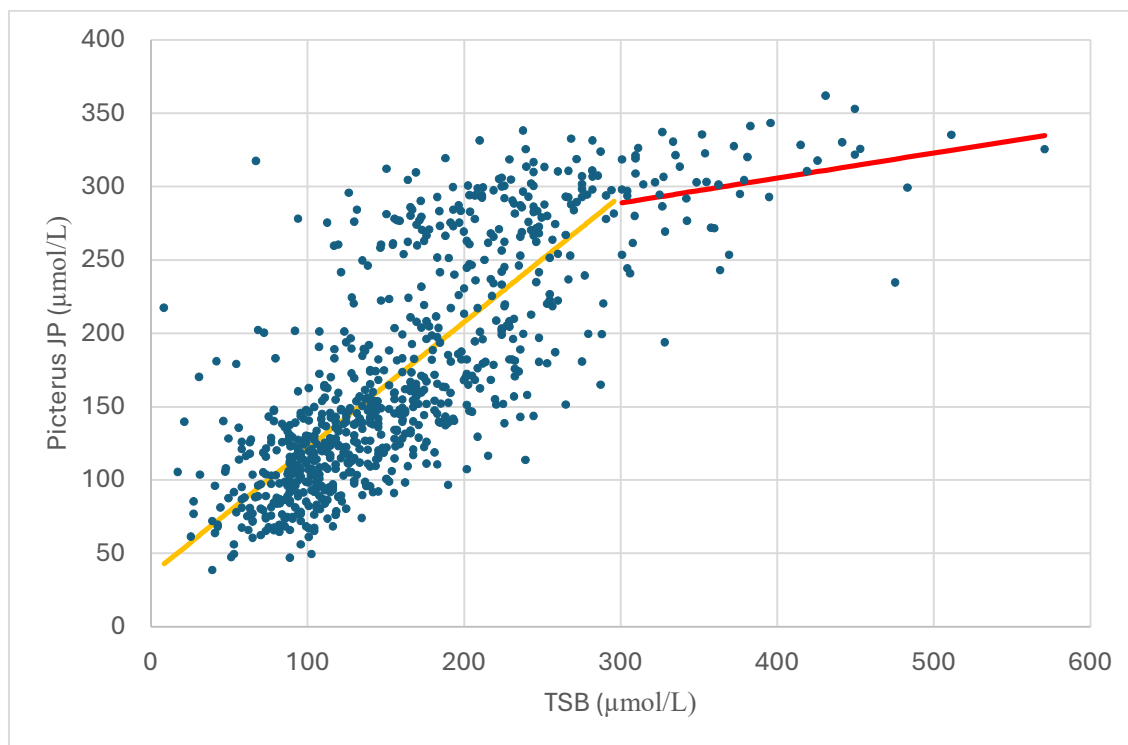


Figure 4. Picterus JP measurements plotted against corresponding TSB values.

The yellow line shows the relationship between the measurement pairs with a TSB below 300 μmol/L ($\text{Picterus JP} = 35.63 + 0.86 \times \text{TSB}$).

The red line shows the relationship between the measurement pairs with a TSB below 300 μmol/L ($\text{Picterus JP} = 237.89 + 0.17 \times \text{TSB}$).

4.3 Agreement analysis

Agreement between the two methods of measurement was assessed using the method of Bland and Altman.

Figure 5 shows the difference between each pair of measurements ($\text{Picterus JP} - \text{TSB}$) plotted against the mean of each pair. The mean of the differences (bias) is 9.39 μmol/L. Picterus JP is, on average 9.39 μmol/L higher than TSB. There is considerable scatter around this bias with 95% limits of agreement between -95.3 μmol/L and 114.11 μmol/L. These are wider than the limits of agreement seen in studies of Transcutaneous Bilirubinometry.

The lower limit of agreement is the most clinically important in this analysis as underestimation of TSB increases the risk of not recognising a baby with significant jaundice. TSB will be underestimated by at least the lower limit of agreement in 2.5% of measurements. The reported lower limit of agreement reported in TcB evaluations ranges between -45 μmol/L and -77 μmol/L (8, 9, 10, 11) and -95.3 μmol/L with Picterus JP.

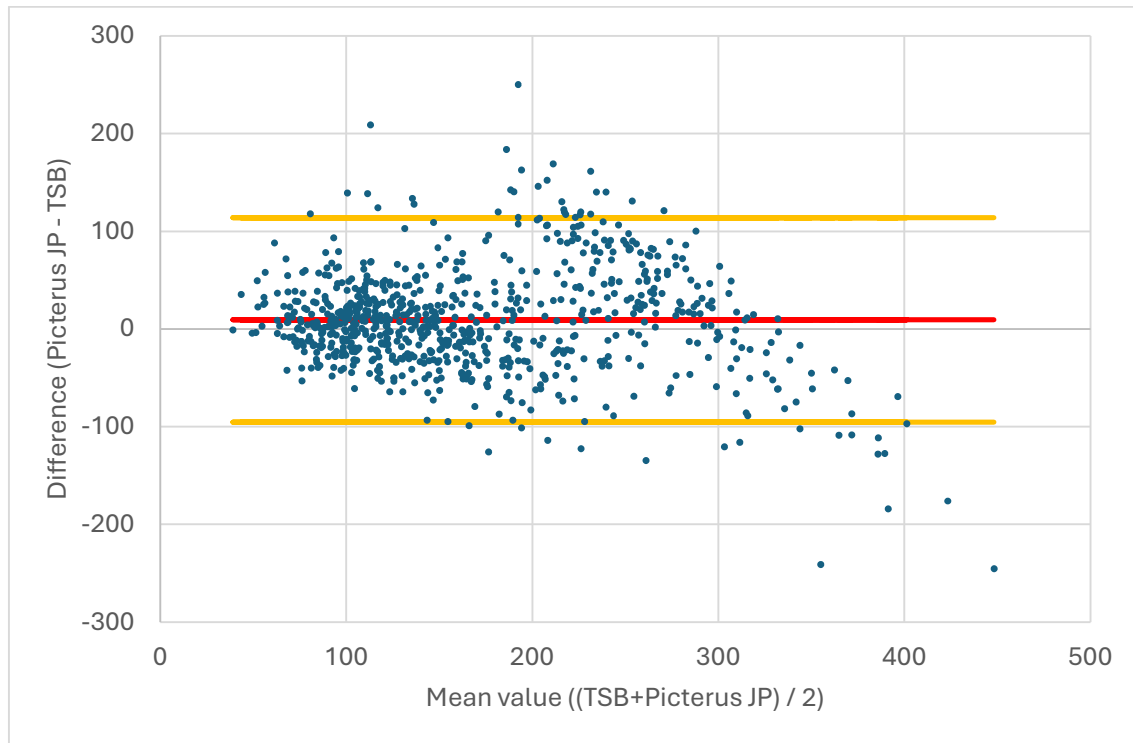


Figure 5. Bland Altman Agreement plot for all paired measurement. The red line shows the mean difference and the orange lines show the 95% limits of agreement.

As seen in the Bland Altman Agreement plot, the relationship between the two measurements appears to be different for measurement pairs with a TSB above 300 $\mu\text{mol/L}$ and with a TSB below 300 $\mu\text{mol/L}$.

For measurement pairs with a TSB below 300 $\mu\text{mol/L}$ the mean difference is 14.86 $\mu\text{mol/L}$, meaning that the Picterus JP measurement is, on average 14.86 $\mu\text{mol/L}$ higher than the TSB measurement (Figure 6). There is significant scatter around this bias, the 95% limits of agreement are between -81.7 $\mu\text{mol/L}$ and 110.59 $\mu\text{mol/L}$.

For measurement pairs with a TSB above 300 $\mu\text{mol/L}$ the mean difference is -63.6 $\mu\text{mol/L}$, meaning that the Picterus JP underestimates the TSB measurement by an average of 63.3 $\mu\text{mol/L}$ (Figure 7). There is significant scatter around this bias, the 95% limits of agreement are between -177.9 $\mu\text{mol/L}$ and 50.7 $\mu\text{mol/L}$. This is also shown in Figure 6.

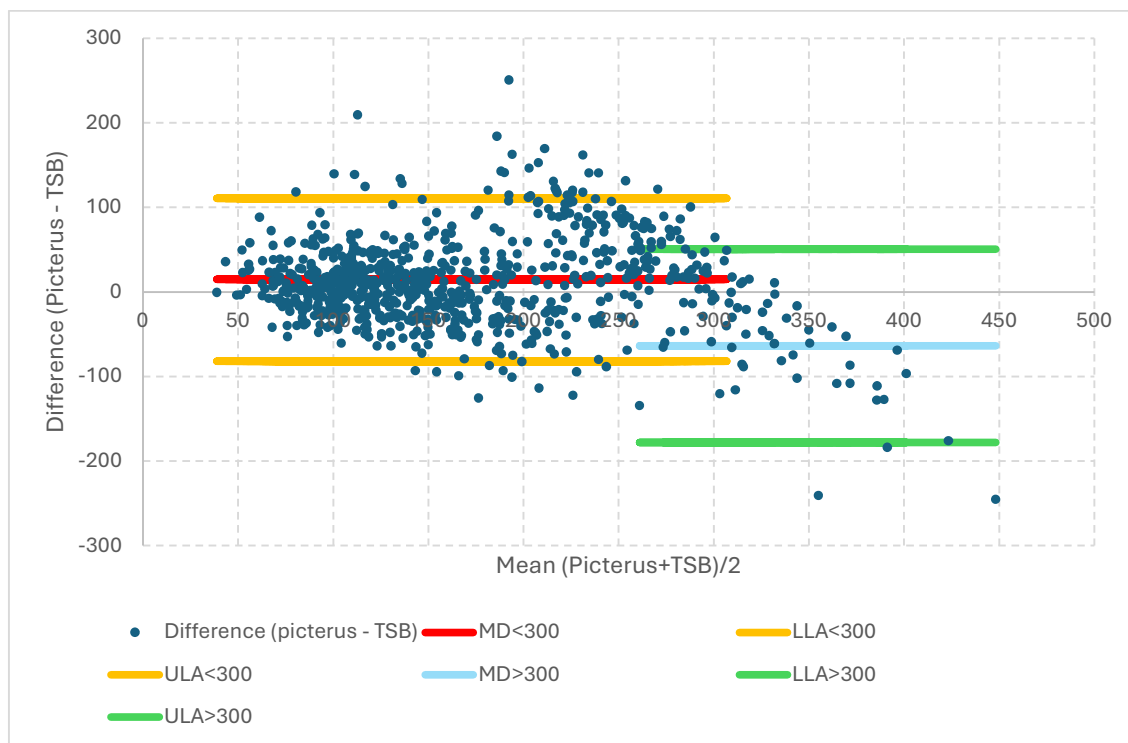


Figure 6. Bland Altman Agreement plot for all paired measurement with a TSB below 300 $\mu\text{mol/L}$. and above 300 $\mu\text{mol/L}$. For TSB measurements below 300 $\mu\text{mol/L}$, the red line shows the mean difference and the orange lines show the 95% limits of agreement. For TSB measurements above 300 $\mu\text{mol/L}$, the blue line shows the mean difference and the green lines show the 95% limits of agreement

The fall off in precision at higher levels of TSB illustrates the hazard of using this system to measure TSB as active treatment decisions are made in this range and the risk of bilirubin encephalopathy rises as the TSB reaches and exceeds 400 $\mu\text{mol/L}$. Like TcB, Picterus JP can be used for screening purposes only.

4.4 The impact of skin pigmentation on the precision of Picterus JP Jaundice pro measurements.

Non-invasive TcB has been used to estimate TSB, but there are concerns about lack of precision in babies with darker skin (3, 5, 6,7).

As described above, the “red channel” (R-channel) of the image obtained by the Picterus JP system provides an objective surrogate marker of skin pigmentation. Images taken from babies with a darker skin have a lower r-channel value.

In order to assess the impact of skin pigmentation on the precision of Picterus JP measurements, the relationship between the “red-channel” (r-channel) of the Picterus JP image for each individual and the difference between two measurements (Picterus JP – TSB) was explored. This relationship was examined by Pearson’s correlation and simple linear regression. R-channel data were available for 786 of the 790 subjects.

There is a weak, but statistically significant negative correlation between the difference between the two measurements and the r-channel value ($n=786$, $r=-0.13$, $p=0.0003$) (Figure 7). This implies that precision is affected by increasing skin pigmentation, with a potential resulting over-estimation of TSB in the darkest skinned babies.

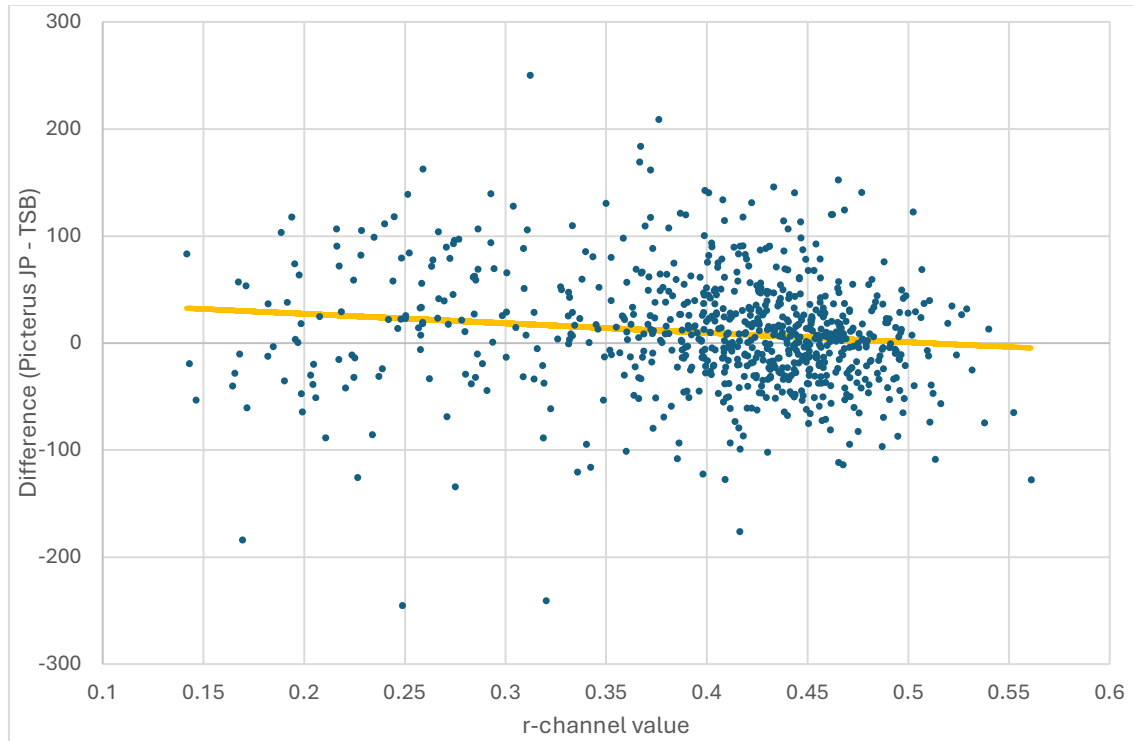


Figure 7. The difference between the two measurements (Picterus JP-TSB) plotted against the r-channel value of each subject. The orange line represents the regression line.

Linear regression analysis gave an r -squared value of 0.017, so only 1.7% of the variability in the precision of Picterus JP could be attributed to variability in the r -channel value. The equation for the regression line is: Difference (Picterus JP-TSB) = $45 - 88.5 \times (r \text{ channel})$. R -squared = 0.017

So (on average) the precision of Picterus JP versus TSB increases by $8.85 \mu\text{mol/L}$ with every increase of 0.1 R -channel value unit. The range of R -channel values between the darkest and lightest babies in this cohort was 0.419 units so the precision of Picterus JP may have improved by $37.1 \mu\text{mol/L}$ in the lightest skinned baby compared to the darkest skinned baby.

Reduced precision in darker skinned babies, with over-estimation, would mean that darker skinned babies are less likely to have significant jaundice missed by Picterus JP. It could also mean that darker skinned babies are less likely to see potential benefits of the Picterus JP system, such as reduced blood tests for TSB evaluation.

However, as most babies were not at the extremes of R -channel value, any impact of skin pigmentation of Picterus JP precision within any individual would be smaller than the maximum value estimated above. The range of TSB in the subjects of the study was $562 \mu\text{mol/L}$ and the 95% limits of agreement between Picterus JP and TSB are between $-95.3 \mu\text{mol/L}$ and $114.11 \mu\text{mol/L}$. Given all of these considerations the reduction of precision of Picterus JP measurements seen in babies with darker skin tones is unlikely to be of clinical significance.

4.5 Picterus JP Jaundice Pro as a screening device

Picterus JP measurements do appear to be reasonable indicator of jaundice severity so it is possible that it could be used as a screening tool to identify babies who require evaluation of their jaundice with TSB. For the purpose of screening, a test result must be reduced to a binary result of “screen positive” or “screen negative”.

TSB is the gold standard for clinical decision making in neonatal jaundice. One of the challenges of assessing Picterus JP as a screening tool is that the TSB thresholds for babies needing intervention vary by gestational age and across time (2,3). These treatment thresholds are well accepted, but not based on any rigorous scientific evidence.

TcB is a well-established non-invasive method that is used to screen for neonatal jaundice in this way. There are a number of different manufacturers of TcB devices, and it is likely that each of these devices will perform differently, although NICE and AAP guidelines seem to accept that any TcB device can be used for this purpose. Several studies have examined the precision of some of these TcB devices as a measure of TSB and all report a fairly close mean difference between the two measurements with considerable scatter so that the lower limit of agreement has been reported to be in the order of approximately $-45 \mu\text{mol/L}$ and $-77 \mu\text{mol/L}$ (i.e. on 2.5% of occasions the TcB will underestimate the TSB by at least 45 to $77 \mu\text{mol/L}$) (8,9 10,11).

Guidance from the National Institute for Clinical Excellence (NICE) is that TcB should be measured in all babies with jaundice after 24 hours with a gestation of 35 weeks or more (3). This guidance recommends that TSB should be measured if the TcB value exceeds $250 \mu\text{mol/L}$ or is at or above the treatment threshold (for babies in whom the treatment threshold is below $250 \mu\text{mol/L}$). From the studies of TcB precision, a TcB threshold of above $250 \mu\text{mol/L}$ should identify most babies with a $\text{TSB} > 300 \mu\text{mol/L}$.

Guidance from the American Academy of Paediatrics (2) is that TcB should also be used to assess jaundiced babies and that TSB should be measured if TcB is $\geq 15 \text{ mg/dL}$ ($256.5 \mu\text{mol/L}$) or if the TcB exceeds or is within 3 mg/dL ($51.3 \mu\text{mol/L}$) of the phototherapy treatment threshold.

In making clinical decisions for the management of neonatal jaundice, it is imperative that sensitivity of the screening test is prioritised because of the serious consequences of a false negative test (missed significant jaundice).

Two strategies for screening arise from this.

The first is to test whether Picterus JP can identify a clinically meaningful level of TSB that most clinicians would consider to require intervention and to use that Picterus JP result as the definition of “screen positive” or “screen negative” (Method 1 below).

The second is to produce a “screening chart” with different values of Picterus JP being “screen positive” or “screen negative” in different situations. This has been performed in the section entitled Method 2 below using the NICE phototherapy thresholds for babies born at 35 weeks or more. It was not possible to repeat this exercise for the AAP thresholds as the need for phototherapy in those guidelines is affected by the presence or absence of neurological risk factors and these data have not been collected in this study.

Method 1. Using Picterus JP to identify a clinically meaningful level of TSB.

Detection of TSB > 250 $\mu\text{mol/L}$ by Picterus JP

Several studies evaluating TcB have tested the screening value of TcB to detect TSB of >250 $\mu\text{mol/L}$ as they considered that clinicians would require a more accurate measurement of jaundice using TSB at that level (9, 10, 11, 12).

Sensitivity and specificity for the detecting TSB > 250 $\mu\text{mol/L}$ were calculated for each value of Picterus JP and a receiver operator curve (ROC) was constructed. The ROC is shown (Figure 8)

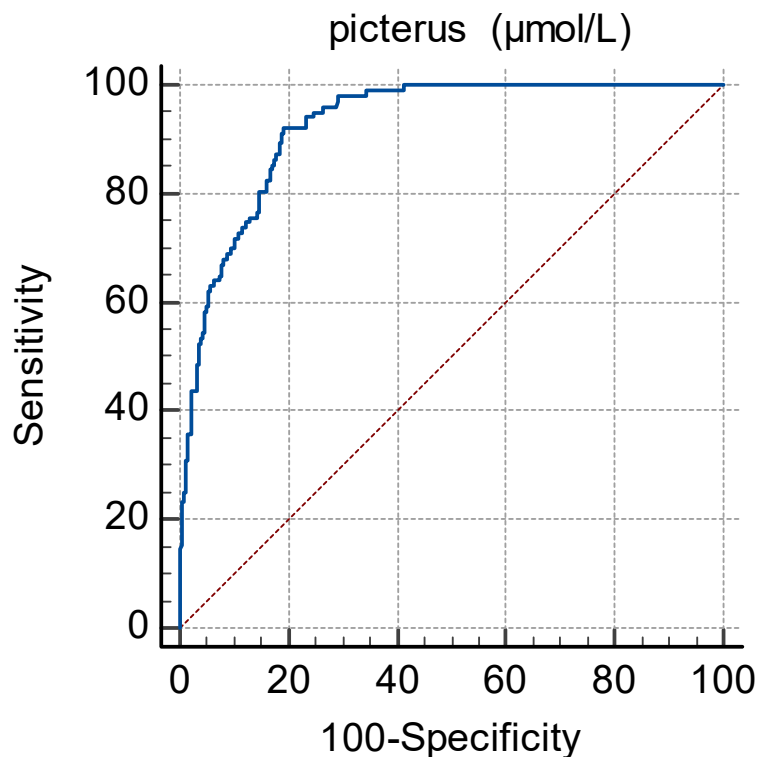


Figure 8. ROC for the detection of TSB > 250 $\mu\text{mol/L}$ by Picterus JP.

The area under the ROC is 0.93.

A Picterus JP measurement of 151.2 $\mu\text{mol/L}$ gives 100% sensitivity and 58.7% specificity.

Using this value gives:

No false negatives (all babies who have a TSB > 250 $\mu\text{mol/L}$ are correctly identified)

103 true positives

284 false positives (284 babies who were identified as having a TSB > 250 $\mu\text{mol/L}$ actually had a TSB < 250 $\mu\text{mol/L}$ (73% of the “screen positive” babies)

403 true negatives (403 babies were correctly identified as having TSB < 250 $\mu\text{mol/L}$).

From this we can say that, if the purpose of the test was to identify babies who required a blood test to detect TSB>250, all positive babies were identified correctly and 51% of the babies were correctly identified as not needing a blood test. This does not equate to a 51% reduction in blood tests as some of the babies recruited to each study were having blood taken for reasons other than jaundice evaluation.

Detection of TSB>300 $\mu\text{mol/L}$ by Picterus JP

Given the imprecision of TcB, the NICE recommendation to measure TSB when TcB is above 250 $\mu\text{mol/L}$ is effectively using TcB to screen for a TSB>300 $\mu\text{mol/L}$.

Using the same methodology another ROC was created for the detection of TSB >300 $\mu\text{mol/L}$ using Picterus JP (fig 9).

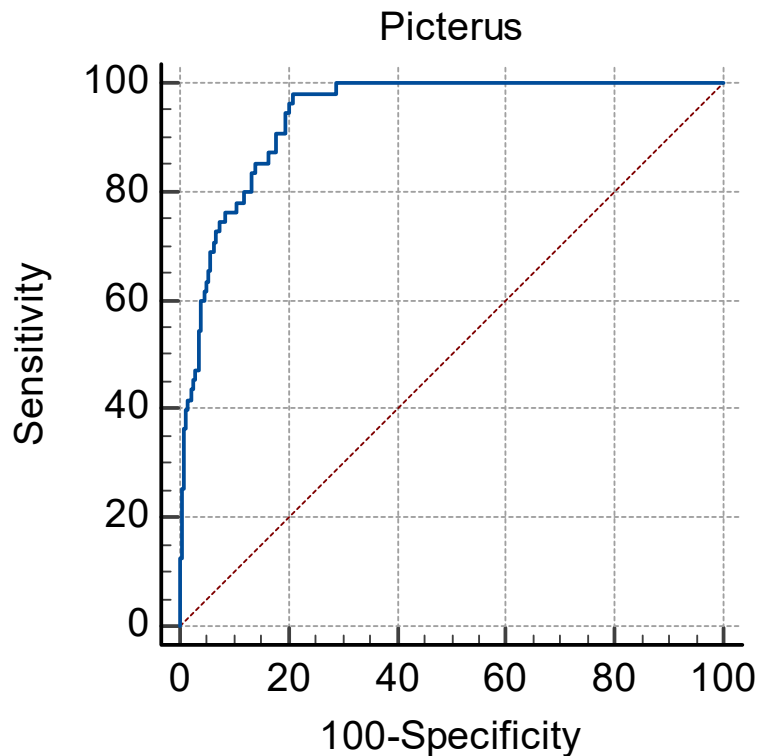


Fig 9. ROC for the detection of TSB>300 $\mu\text{mol/L}$ using Picterus JP.

The area under the curve is 0.941

A Picterus JP value of >193 $\mu\text{mol/L}$ gives sensitivity of 100% and specificity of 71%.

Using this value gives:

- No false negatives

- 55 true positives

- 213 false positives (79% of "screen positive" babies had a TSB<300 $\mu\text{mol/L}$)

522 true negatives (66% of babies were correctly identified as having a TSB<300 $\mu\text{mol/L}$ and, therefore not requiring a blood test for TSB measurement.

From this we can say that, if the purpose of the test was to identify babies who required a blood test to detect TSB>300, all positive babies were identified correctly and 66% of the babies were correctly identified as not needing a blood test. This does not equate to a 66% reduction in blood tests as some of the babies recruited to each study were having blood taken for reasons other than jaundice evaluation.

Method 2. Constructing Picterus JP curves based on the NICE phototherapy charts.

Method 2a – screening to detect which babies require phototherapy

The NICE phototherapy threshold increases on each day until day 4 of life and subsequently remains at this level. The thresholds increase with increasing gestation. These value for these thresholds (in $\mu\text{mol/L}$) at the end of each day are shown in Table 3.

Gestation	24H	48H	72H	96H
35	110	180	250	250
36	115	190	260	260
37	120	195	270	270
38+	200	250	300	350

Table 3. TSB thresholds to start phototherapy by gestation according to guidance from NICE.

For the purposes of this evaluation, the ability of the Picterus JP system to screen for each of these thresholds was assessed by producing a series of ROC curves as described above. The “Picterus JP thresholds” based on these are shown in Table 4.

Gestation	24H	48H	72H	96H
35	68.1	96.3	151.2	151.2
36	68.1	106.9	151.2	151.2
37	73.8	106.9	164.7	164.7
38+	106.9	151.2	193	233.9

Table 4. Picterus JP measurement values to identify babies who require TSB assessment as they are likely to require phototherapy.

From the data in Table 4 a series of charts were produced to show the Picterus JP threshold line against the NICE phototherapy threshold line. These charts appear as an appendix to this paper (charts A1 to A4).

To assess the impact of these charts on the number of blood tests that would have been performed if they had been used, phototherapy threshold status was determined from the TSB measurement of each paired measurements for each subject using the NICE gestation specific charts.

Picterus JP threshold status was also determined using the charts developed.

TSB positive results (i.e. those above the phototherapy line) were classified as Picterus JP positive or negative depending on whether they were above or below the Picterus JP threshold. The same was done for TSB negative results. The results are shown in Table 5. The system had

100% sensitivity to detect babies with TSB above the NICE phototherapy guideline, with a specificity of 38.4%.

		TSB above phototherapy line	
		Positive	Negative
Picterus JP above threshold	Positive	93	420
	Negative	0	277

Table 5. Classification of each pair of measurements by Picterus positivity/negativity and TSB positivity/negativity for detection of the need for phototherapy.

The sensitivity of the system to identify babies who required phototherapy was 100% and the specificity was 39.7%.

There were 93 babies who required phototherapy. All of these were correctly identified as being in need of a blood test from the Picterus JP thresholds (100% True Positives, 0% False Negatives).

There were 697 babies who did not require phototherapy.

Of these 277 (39.7%) were correctly identified as not requiring a blood test by the Picterus JP charts.

The other 420 who did not require phototherapy were identified as requiring a blood test by the Picterus JP charts.

So, all babies who required phototherapy were correctly identified by the system. 277 babies (35% of the whole cohort) could have avoided a blood test if the Picterus JP charts had been used to determine the need for a blood test. It is not possible to be sure exactly how many babies would actually have avoided a blood test from these data, however, as each of the studies included babies who were having blood tests for reasons other than jaundice evaluation and these tests would still have been performed regardless of the Picterus JP result.

Method 2a – screening to detect which babies require phototherapy or follow up TSB measurement.

NICE also recommends that in a baby of 38 weeks gestation or above who has not received phototherapy, if the TSB is less than 50µmol/L below the phototherapy line, a repeat TSB should be collected within 18 or 24 hours, depending on the presence of defined risk factors. These “follow up thresholds” are shown in Table 6.

Gestation	24H	48H	72H	96H
38+	150	200	250	300

Table 6. TSB thresholds at which to perform repeat TSB measurement in 18 to 24 hours according to guidance from NICE.

A further set of ROC curves was developed to identify the Picterus values that identified these thresholds with a sensitivity of 100% based on these another chart was produced that identified the need for either phototherapy or a repeat TSB measurement. This chart appears in the appendix (chart 5).

The results were reclassified as Picterus positive or negative (above or below the Picterus threshold) and also TSB positive (TSB either above the phototherapy line or indicating a repeat

TSB was required) or negative. The classification of the data into these groups is shown in Table 7.

		TSB above phototherapy line or requiring repeat TSB	
		Positive	Negative
Picterus JP above threshold	Positive	187	448
	Negative	7	148

Table 7. Classification of each pair of measurements by Picterus positivity/negativity and TSB positivity/negativity for detection of the need for phototherapy or repeat TSB.

The sensitivity of the system to identify that a baby required phototherapy or a repeat TSB was 96.4%, the specificity was 24.8%.

As well as the 93 babies who required phototherapy, there were another 101 who required a follow up TSB. 94 of these had a Picterus JP measurement value above the Picterus line, so would have been correctly identified as in need of a repeat TSB.

155 babies had a Picterus result below the threshold, so 19.6% of babies would have avoided a blood test if these charts had been used, although 7 of these would have been within 50 of the phototherapy threshold and would have required repeat blood tests.

So 3.6% of babies who required intervention would have been missed, all of these were babies who required repeat TSB only.

Screening for significant jaundice with Picterus JP

These data and analyses suggest that it is possible to detect all babies who are above the phototherapy threshold using Picterus JP. There are a number of false positives using this approach, but there is still the potential to reduce the number of blood test performed.

If the aim is to detect babies who require phototherapy *or* a repeat TSB (as per NICE recommendations) then 96.4% of babies are correctly identified. The 3.6% who were missed required repeat TSB only, not phototherapy. Again, there is clearly potential to reduce blood tests with this approach.

5. Conclusions

Like TcB, Picterus JP is a non-invasive method to assess jaundice and lacks the precision to measure TSB accurately. It is licensed as a medical device on the European Medical Device Regulation to be used for neonatal jaundice screening.

The impact of skin pigmentation on the precision of Picterus JP measurements appears to be of no clinical consequence.

Picterus JP measurements can be used to screen babies to identify which require a blood test for TSB estimation. The first screening algorithm described in this paper has 100% sensitivity to

detect babies in this cohort who require phototherapy according to the NICE guidelines. The second algorithm has a 94.6% sensitivity to detect babies who require treatment with phototherapy or a repeat TSB measurement.

It is not possible from these data to assess accurately how effective Picterus JP would be in reducing blood tests etc. The estimates, based on our data are that 20% to 35% of blood tests could have been avoided, although this could be an overestimate. Estimates of TSB reduction predicted from TcB studies ranged from 20% to 60% (8, 11, 12). Introduction of a TcB screening policy into clinical practise in a large US setting has been shown to reduce blood samples for TSB by 22% (14).

Picterus JP appears to be a viable option for screening neonates for the need for TSB. The advantages of Picterus JP compared to TcB are the lower cost, the ease of deployment, the lack of a need to recalibrate the equipment and the reassurance about similar performance in babies with darker skin. Unfortunately, the benefits in terms of knowing what the reduction in TSB etc could be achieved are not known and not knowable from these data. A crude estimate of this reduction would be 20% to 35% but this likely to be an overestimate as many of the 'avoided' blood tests would not have been performed anyway as the subjects were not requiring jaundice evaluation. The lower the TSB reduction that the system achieves, the less likely it will be to adopted into clinical practise. I expect that a reduction to as low as 10-15% would make the system unattractive to clinicians.

These data should be considered as a "development cohort". It is not possible to be certain that the conclusions reached will hold true in another cohort of babies. The methodology developed should be tested in a "Validation cohort". If this is performed only in babies who require a blood test for the assessment of their jaundice, then it will also be possible to quantify the likely benefit from this system in terms of reduction in blood tests etc.

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8. Appendix

Picterus JP threshold charts

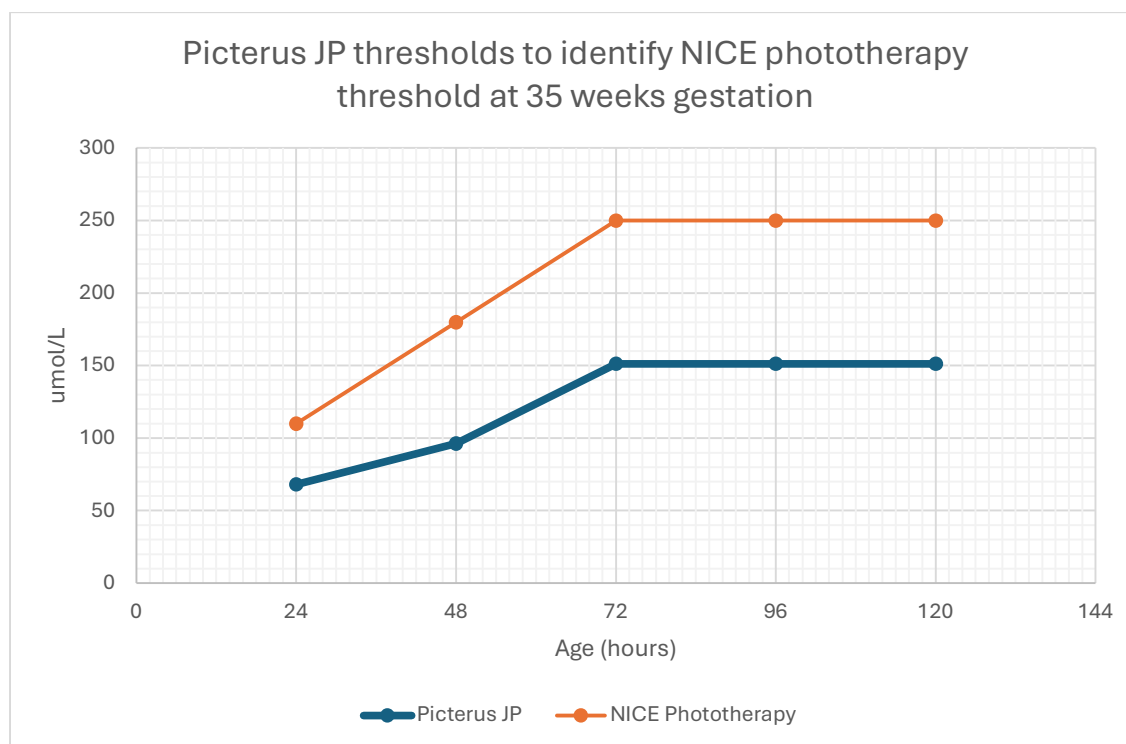


Chart A1 – Picterus JP Thresholds to identify the need for phototherapy at 35 weeks gestation

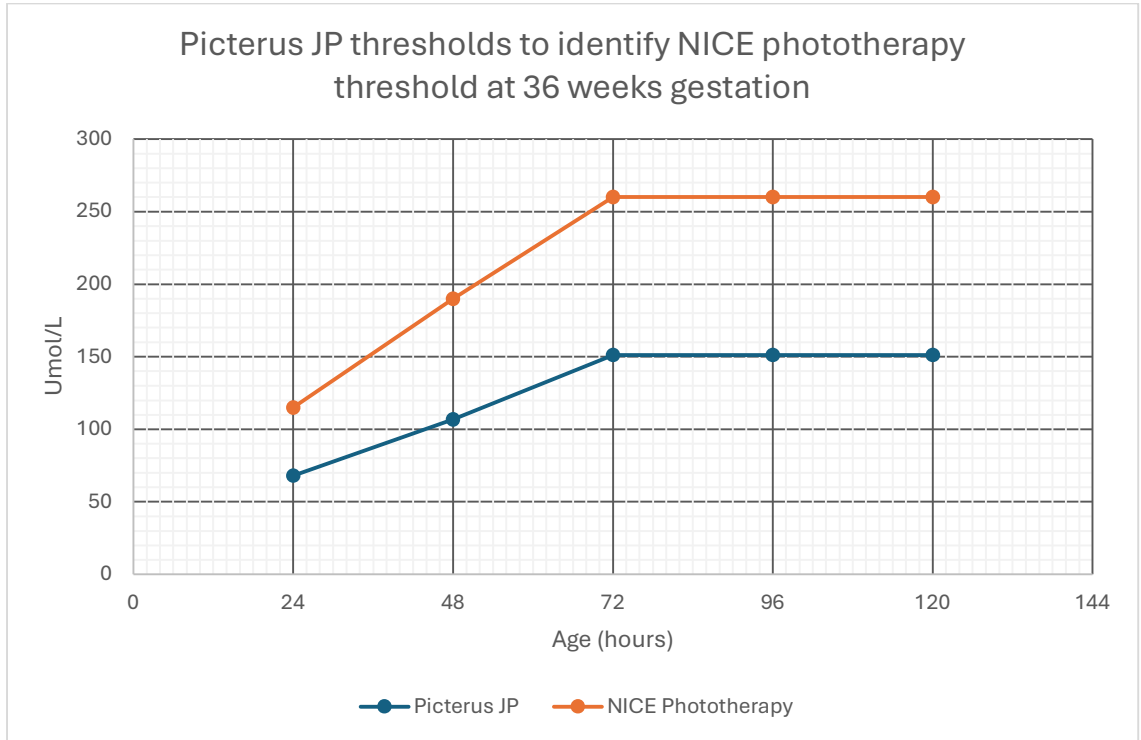


Chart A2 – Picterus JP Thresholds to identify the need for phototherapy at 36 weeks gestation

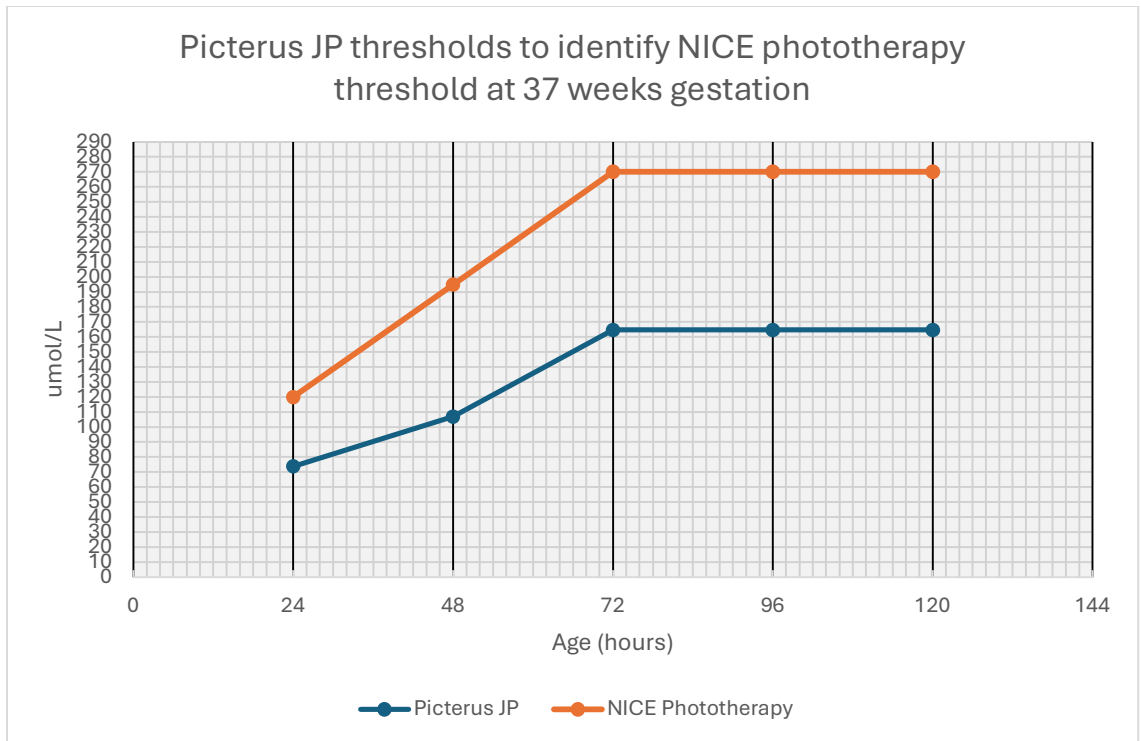


Chart A3 – Picterus JP Thresholds to identify the need for phototherapy at 37 weeks gestation

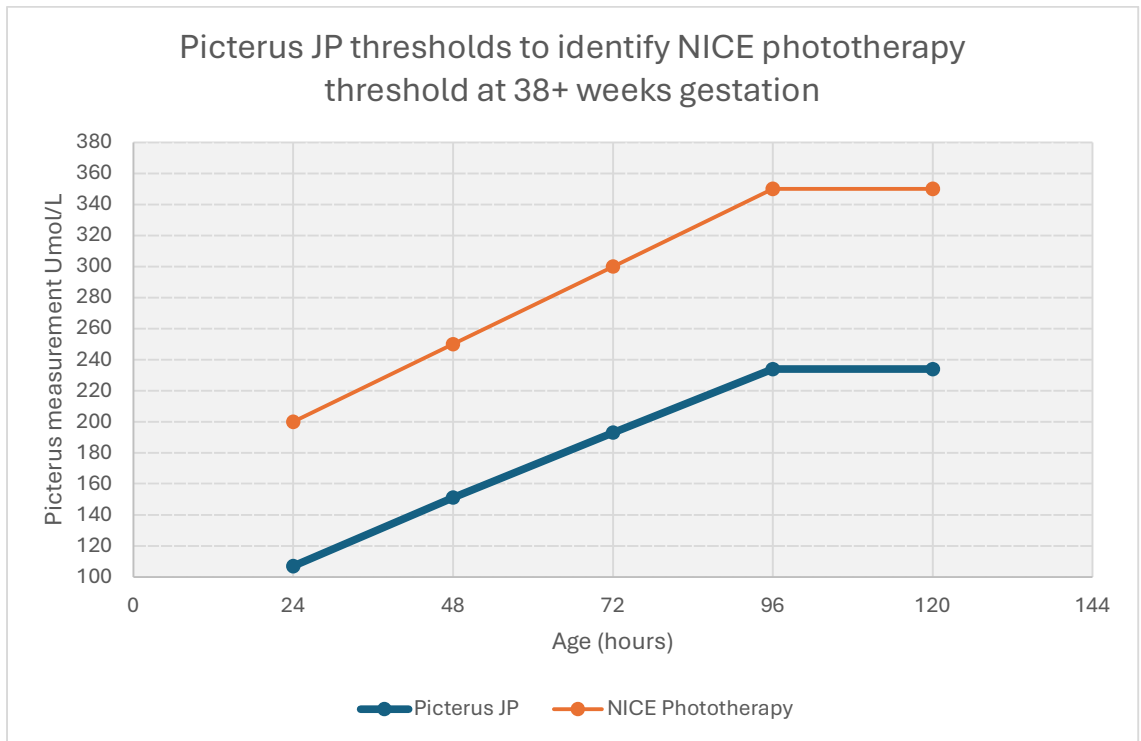


Chart A4 – Picterus JP Thresholds to identify the need for phototherapy at 38+ weeks gestation

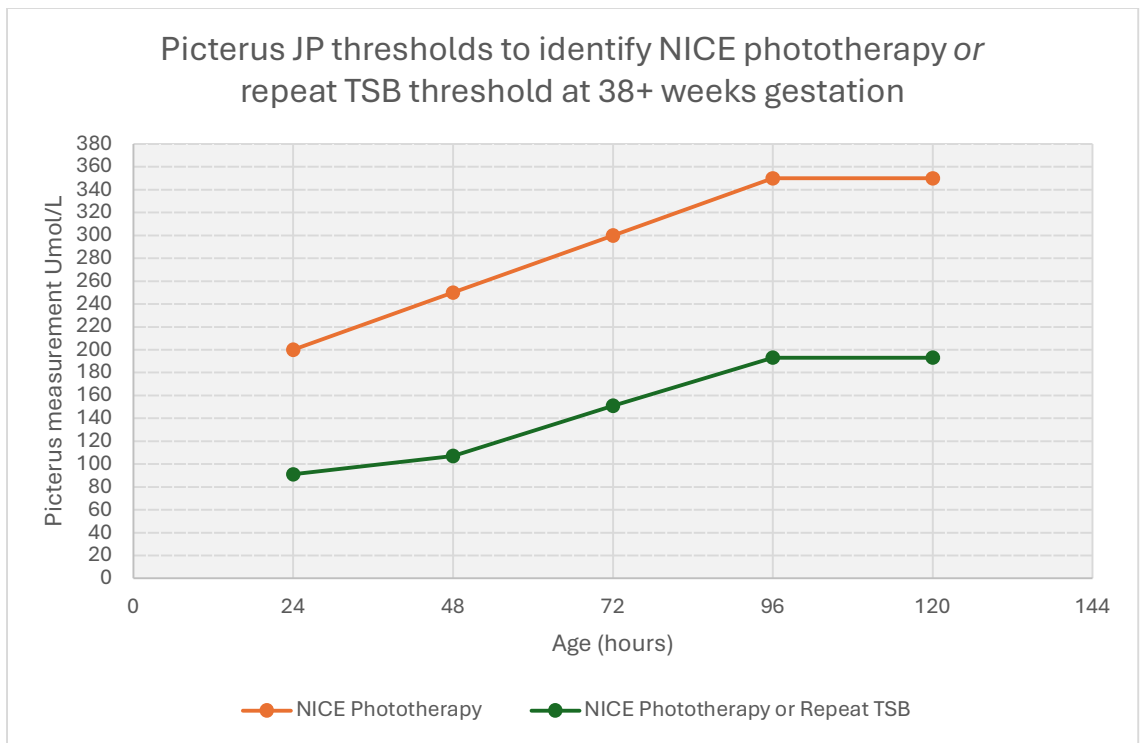


Chart A5 – Picterus JP Thresholds to identify the need for phototherapy or the need for repeat TSB measurement at 38+ weeks gestation