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Methods for Determining Bilirubin Level in Neonatal Jaundice Screening and Monitoring: A Literature Review

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ABSTRACT

Physiological jaundice in newborns occurs after the first 24 hours of life due to the increasing level of bilirubin in the blood circulation resulting in the yellowish discoloration of the skin and sclera. Severe jaundice with toxic bilirubin level may lead to brain damage caused by the bilirubin staining of the central nervous system, medically termed as kernicterus. Currently, there are various measurement techniques in monitoring bilirubin level in cases of neonatal jaundice. This paper aimed to provide a comprehensive review of various methods of non-invasive screening and monitoring of neonatal jaundice which includes the light wavelength absorption or reflectance technique, optical technique, electronic equipment and image processing technique.

Keywords: Bilirubin, Infant, Jaundice, Kernicterus, Neonatal, Newborn.

1. INTRODUCTION

Jaundice or *icterus*, refers to the yellowish discolouration of the skin or in the whites of the eye. This condition is fairly prevalent among the newborns due to their immature liver's inefficiency to metabolise bilirubin. Up to 60% of term infants and 80% of preterm infants were found to develop neonatal jaundice in their first week of life and 10% of breastfed newborn were commonly jaundiced even up to four weeks old [1].

Jaundice may be grossly visible when the serum bilirubin level exceeds 2.0 to 2.5 mg/dl [2]. Bilirubin is a water-soluble, tetraphyrrolic yellowish pigment compound found in the blood and requires an enzyme-mediated glucuronidation process in the liver for proper excretion [3]. Additionally, bilirubin is the by-product of haemoglobin catabolism. Newborns have a higher rate of haemoglobin catabolism as compared to older children or adults because of their relatively higher haematocrit level and red blood cell volume per body weight coupled with their significantly shorter fetal red blood cell life span as compared to adults (70 to 90 days vs. 120 days) [4]. Although neonatal jaundice is a fairly common encounter in clinical practice, it indisputably requires an early detection for timely management. Hyperbilirubinemia is a condition when the serum bilirubin concentration reaches higher than 250 µmol/l [5] in which without proper management can reach toxic levels and further results in irreversible neurological damage.

Toxic levels of bilirubin may lead to *kernicterus*, a rare condition but is serious and entailed irreversible neurological sequelae characterised by athetoid spasticity, visual abnormalities, and sensorineural hearing loss among its survivors [6].

Management of neonatal jaundice is guided through multiple variables which include the newborn's age, weeks of gestation and the serial bilirubin level [1]. Clinical monitoring of

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neonatal jaundice routinely involves a specialised graph called the Bhutani nomogram [7] as shown in Figure 1.

This nomogram delineates the risk strata into low-risk, low-intermediate and high-intermediate risk based on the presence of risk factors such as the gestational age at birth and the birth weight, together with the hour-specific serum bilirubin values [7].

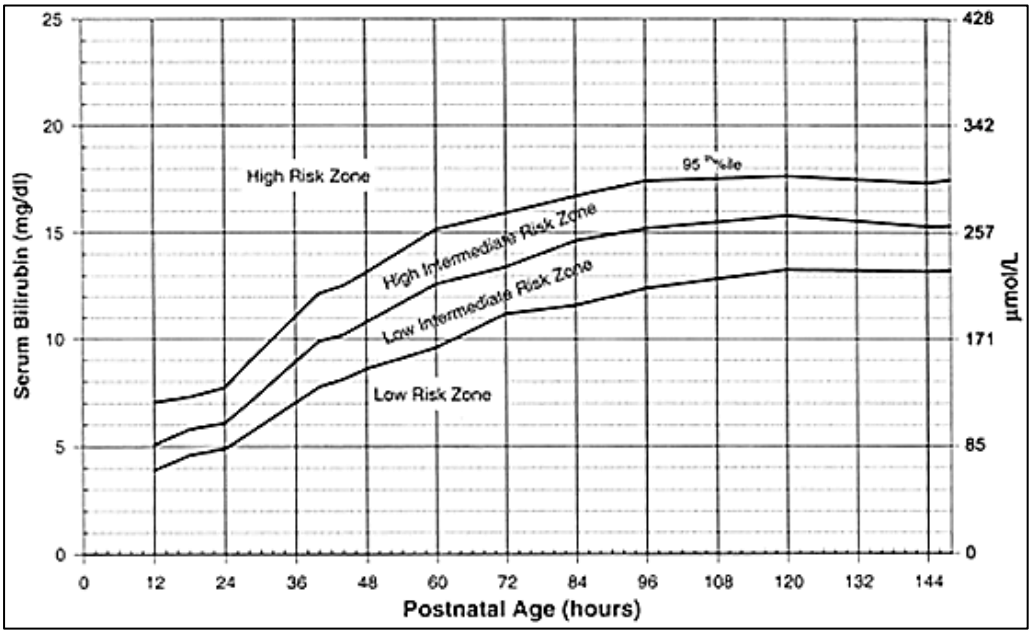

Figure 1. Bhutani nomogram [7].

Phototherapy is the current mainstay of treatment in cases of neonatal jaundice. Phototherapy uses the blue light source of 450 nanometer (nm) wavelengths. Absorption of the light source from the skin will further cause structural isomerization of the bilirubin molecule into a more easily excreted form to be released in the stool and urine. Phototherapy is the common method applied in the clinical setting in the management of normal and low-risk newborn. Unfortunately, some newborns respond poorly to phototherapy and may require exchange transfusion (ET) to reduce the rising bilirubin level. ET is an invasive treatment procedure involving the replacement of a calculated volume of the newborn's blood with a donor's blood in an attempt to reduce the circulating bilirubin level.

Visual assessment is the easiest available, non-invasive method to distinguish the presence of jaundice in newborn. Kramer's rule indicates that neonatal jaundice begins from the newborn's head, hence observation should be made from the face towards the feet as the level rises [8]. The observation is done by applying appropriate pressure on the neonatal forehead to remove the blood from the surface capillary, further revealing the intensity of the underlying yellowish hue of the skin, if present [9]. Kramer's rule describes the exponential relationship between the serum bilirubin level and the progression opacity of the skin discoloration.

However, this method is not reliable for jaundice monitoring as it is operator-dependent and is affected by the newborn' skin colour. Table 1 and Figure 2 depict the correlation between the visual assessment and the estimated serum bilirubin values.

Table 1 Kramer's rule visual assessment of neonatal jaundice (Ministry of Health, 2015)

Area of the Body	Level	Range of Serum Bilirubin	
		µmol/L	mg/dL
Head and neck	1	68-133	4-8
Upper trunk (above umbilicus)	2	85-204	5-12
Lower trunk and thighs (below umbilicus)	3	136-272	8-16
Arms and lower legs	4	187-306	11-18
Palms and soles	5	≥ 306	≥ 18

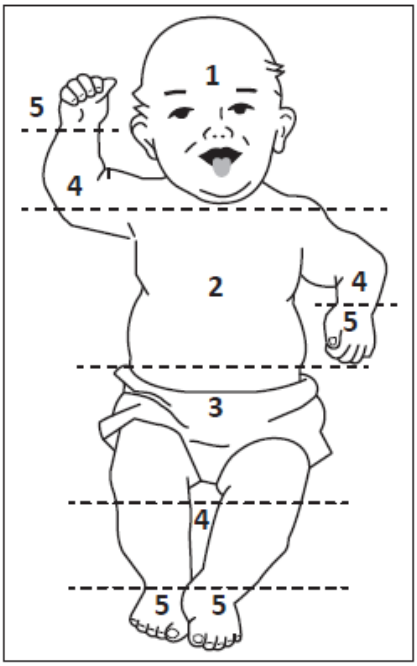

Figure 2. Progression level of skin discoloration in neonatal jaundice [10].

2. LITERATURE REVIEW

2.1 Types of Jaundice

Jaundice is a universal clinical finding in liver disease. Scleral discolouration is a common finding in hyperbilirubinaemia due to the high elastin in the scleral tissue which has a high affinity to bilirubin. The presence of scleral *icterus* indicates a serum bilirubin of at least 50 µmol/l [11]. Jaundice in newborns may well be categorised into two main types; physiological jaundice and pathological jaundice. These classifications are further sub-classified according to the cause of the development of jaundice as different management follows. Examples include the breast-feeding jaundice, breast milk jaundice, hemolytic jaundice and jaundice associated with Glucose-6-phosphate dehydrogenase deficiency [12].

Physiological jaundice is common in newborn, with at least one third of all breastfed infants are clinically jaundiced by their third week of life [13]. Physiological jaundice is due to the liver immaturity to efficiently process the bilirubin molecules for excretion. Physiological jaundice is evident between 24 to 72 hours of life and lasted between four to five days in term newborns while premature newborn may have its peak bilirubin level by day seven of life [12]. Physiological jaundice typically disappears by 10 to 14 days of life. Mothers are naturally advised to continue breast-feeding frequently at deemed adequate intervals of two to three-

hourly before the total serum bilirubin (TSB) levels eventually declines over a period of time [14].

Pathological jaundice on the other hand is commonly due to the increased in the breakdown of red blood cells, further increasing the bilirubin by-product. This process is called *hemolysis*. Non-physiologic bilirubin level is defined if the bilirubin concentration exceeds 5 mg/dl on first day of life in term newborn, 10 mg/dl on the second day or 12-13 mg/dl afterwards [14].

Breast-feeding jaundice is due to poor feeding in the early neonatal life, leading to dehydration and low caloric supply [15]. Breast-feeding jaundice usually appears between 24 to 72 hours of life, peaks by 5 to 15 days of life and commonly disappears by the third week of life [14]. Nevertheless, some newborns may have breast-feeding jaundice persist for as long as 12 weeks of life before its spontaneous resolution [16]. Mothers are encouraged to increase the frequency of feeding and a supplementary feeding with formula is suggested if the problem is due to the lack of milk production.

Hemolytic jaundice occurs due to an accelerated breakdown of red blood cells, thus leading to an increase in the production of bilirubin. There are several factors that add risk to *hemolysis* in newborn, including Rhesus hemolytic disease, ABO incompatibility and glucose-6-phospate dehydrogenase (G6PD) deficiency [14]. G6PD deficiency is an inherited condition causing the affected person to be deficient in the enzyme glucose-6-phosphate dehydrogenase. G6PD is important to ensure normal function of the red blood cells and to prevent it from oxidative stress. G6PD deficient individuals are prone to develop anaemia or low haemoglobin level, due to hemolysis resulted from oxidative stress [17].

2.2 Invasive Technique Measurement

Invasive technique is the common method of assessment of total serum bilirubin (TSB) level. This technique requires blood sample to be withdrawn from the newborn with the use of a needle prick. The blood sample will then be stored in the dark to avoid light exposure before being sent to the laboratory for further analysis [8].

Diazo method is a common laboratory technique used in measuring bilirubin. This method is principally based on the different solubility properties of the conjugated and unconjugated bilirubin [18]. However, this method may further underestimate a low level of bilirubin in a given sample. High Pressure Liquid Chromatography (HPLC) method on the other hand, is more superior and has been widely used in the research field. This method allows for a relatively rapid separation and a more precise quantification of the four bilirubin fractions isolated from the sampled serum. These four bilirubin fractions consist of the unconjugated bilirubin, α-bilirubin; monoconjugated bilirubin, β-bilirubin; di-conjugated bilirubin, γ- bilirubin; and a fraction irreversibly bound to protein, δ-bilirubin. Nonetheless, this method does not provide any additional information relevant to the clinical setting as well as the high cost of operation [2].

These two invasive measurements have a turn-around time (TAT) of 30 minutes to perform. These invasive techniques provide the utmost accuracy but may be complicated by infection if poor sterilizing technique, anaemia in repeated blood taking, pain, and distress due to repeated sampling that is required in continuous monitoring [19].

2.3 Non-Invasive Technique Measurement

2.3.1 Light Wavelength Absorption, Reflectance and Optical Technique

Robert had introduced a non-invasive method for determining the bilirubin concentration from the skin reflectance [20]. The method aimed to provide jaundice assessment that is independent of the newborn's skin pigmentation, independent of the spectral distribution of the ambient lighting and the colour of the newborn's enclosure. In the proposed procedure, the newborn's skin is subjected to a light source that is emitted at a plurality at a pre-determined frequency within a range of between 425 nm to 545 nm. The reflected light is collated from a predetermined frequency to further generate electrical signal for further processing. A tungsten-halogen filament lamp is used as the light source.

The light source is attached to a dispersion device that provides a resolved spectral bandwidth for less than 10 nm, a prism type or a grating monochromator. The wavelength-drive mechanism connected to the power supply will determine and control the spectral scan rate and the wavelength that passes through the system. This study used the Jendrassik and Grof's method to compare the bilirubin concentration determined by the proposed method and was evaluated against the bilirubin concentration determined by the conventional laboratory tests among 30 newborn infants. Analysis showed that prediction confidence limit reached up to 95% with an accuracy of ±2 unit over the region 0.5 to 10 mg/100ml concentration. Hence this technique showed a high accuracy and may be ideal in clinical setting due to its non-invasive nature [21].

McEwen and Reynolds [22] on the contrary, had developed a non-invasive method of detection of bilirubin using a pulsatile absorption technique. This study assessed the feasibility of monitoring serum bilirubin concentration using the light absorbance method, a concept that is similar to a pulse oximetry. A nominal pulsatile distance, which is the change in the light path length through a blood segment between the systole and diastole, was calculated using the photodetector output and the graphical absorption coefficients. This study used the Light Emitting Diode (LED) as the light source with five different types of light absorbance calculated using Beer-Lambert Law. The algorithm consists of several variables, including the bilirubin level, methaemoglobin level, oxyhaemoglobin level, carboxyhaemoglobin level and the reduced haemoglobin level. Bilirubin has a higher absorbance at around 480 nm, while pulse oximetry is at 660 nm. Therefore, this method may be practised in the clinical setting for bilirubin detection without the need of a powerful light source.

Kudavelly *et al*. [18] had designed a simpler method with promising accuracy in estimating bilirubin level from the sampled blood. This method used two specific wavelengths at 455 nm and 575 nm in absorption spectrophotometry. The application of spectrophotometer is to evaluate the absorbance peaks of the prepared solutions. National Instruments (NI) Data Acquisition (DAQ) Card has the purpose of capturing the photo detector output. Figure 3 shows the system components of the proposed prototype. A miniature tungsten lamp or a white LED light is used as the light source. The lens in the system will collimate the light rays. Cuvette with the volume of 5 microlitre (μL) and an optical path of $1cm^3$ are used as the sample station to place the sample. Narrow band interference filter of desired wavelength was applied to isolate a narrow band of frequencies from a wider bandwidth signal. The photodetector with a high sensitivity is intended to detect the desired spectrum. This prototype showed an outstanding result as a potential portable bilirubinometer. According to the study coefficient of determination, r^2 between the light absorbance and the concentration of bilirubin of 0.89, it represented a good accuracy between the proposed prototype against the standard measurement.

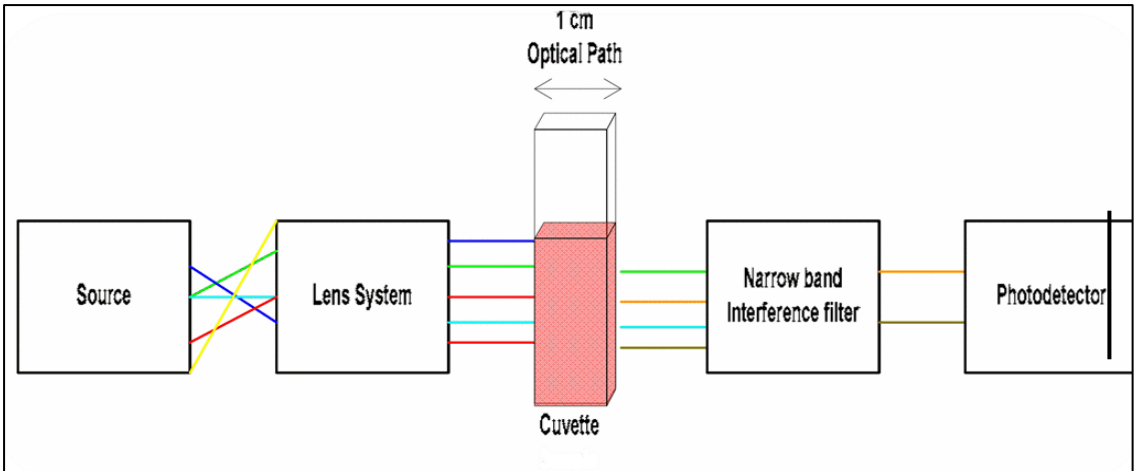

Figure 3. System components of proposed prototype [18].

Penhaker, Kasik, and Hrvolova [23] had designed a method for bilirubin measurement by using a photometric method. This study aimed to design an electronic instrument for measuring bilirubin concentration by applying an optical light transmission through the skin. The study employed the existing knowledge of the different light transmission and absorption through different tissue types, hence utilised the use of two specific wavelengths for its non-invasive bilirubin assessment. The method delivered the results of a maximum error of less than 4% and a relative error of 0.9% when evaluated in seven subjects.

N. Ali *et al*. [24] further introduced a method of optical technique to detect jaundice in the newborn. The concept of light absorption of oxyhemoglobin at different wavelength has been applied by implementing two colours of LED lights, blue and green. The blue LED acts as a light source to determine the bilirubin level while the green LED is used as a reference point to discriminate between bilirubin and haemoglobin. These light sources will pass through the skin and interact with the different molecules and the reflected light will be absorbed by a photodiode for further analysis. The photodiode will measure the reflected light and the data will be sent to the Arduino Uno for processing to determine the bilirubin concentration. Table 2 shows comparison of previous studies based on the different techniques of light wavelength absorption, reflectance and optical technique.

Table 2 Analyses of non-invasive bilirubin studies based on different methods of detection

Author, Year	Method Detection	Range of Light Wavelength (nm)	Results
Robert, 1977	Spectral reflectance from skin	425 to 545	Device and method can determine bilirubin concentration with and accuracy of ±2 unit over the region 0.5 to 10 mg/100ml concentration
McEwen and Reynolds, 2006	Light wavelength absorption	520	Bilirubin shows higher absorbance around 480 nm, while pulse oximetry is performed around 660 nm
Kudavelly *et al*., 2011	Light wavelength absorption	455 and 575	Coefficient of determination (r^2) between light absorbance and concentration of bilirubin was 0.89 which are accurate and to be fitted with regression line
Penhaker *et*	Light wavelength	455 and 575	Results of maximum error for seven

Author, Year	Method Detection	Range of Light Wavelength (nm)	Results
***al.*, 2013**	absorption		subjects less than 4% and the relative error was 0.9%.
N.Ali *et al.*, 2015	Light reflectance from skin	465 to 470	Proposed method are able to measure bilirubin concentration based on the values from voltage reflection absorption that measured by photodiode

2.3.2 Electronic Device or Gadget

BiliCam is a new technology with a low-cost system introduced for detection of jaundice in newborn using a smartphone camera (iPhone 4S) attached to an 8-megapixels camera [25]. The method operates using a calibration card at a size of a standard business card placed on the newborn's abdomen; sternum and forehead before a set of images are captured. The technique, however may subject to error or underestimation of reading in newborn with a darker complexion.

Leung *et al*. [26] had introduced a new technique in screening for neonatal jaundice based on the scleral images using a digital photography. Nikon D3200 camera with the specifications of 24.6 megapixel Complementary Metal Oxide Semiconductor (CMOS) sensor is used with a prime macro lens of 60 mm focal length. The study was validated in 110 newborns' sclera whereby the scleral hue is used to estimate the serum bilirubin level. The captured images were analysed using MATLAB and a customized colour chart was used as a reference. The reference colour was taken as white. This technique was proven to be a promising screening tool in detecting neonatal jaundice especially in cases of TSB level of above 205 μmol/L.

The Receiver Operating Characteristics (ROS) curve from the validation study showed that the sensitivity was 1.00 and 0.50 for the specificity, a better result as compared to the commercial Transcutaneous Bilirubinometry (TcB) such as the *JM-103* and *BiliCheck*. The correlation analysis between the scleral hues and the measured quantification of TSB level was reasonably high with the linear correlation of 0.75, assessed in 110 newborns.

2.3.3 Image Processing Technique

Ali *et al*. [27] introduced a new set of algorithm to diagnose inherited condition of constitutional jaundice which includes Dubin-Johnson syndrome, Gilbert's Syndrome and Rotor's Syndrome. Five clinical features were identified for each disease. The algorithm was composed of two parts, first is the usage of the Wavelet Transform to analyse images and secondly, the calculation of the percentage of grey scales for each images via a histogram. In this technique, three types of image enhancement method are implemented, consisting of image adjustment, logarithmic transformation and histogram equalization. Grow Cut Method is employed in the segmentation of images while Fuzzy Modelling System Structure is utilised for the classification to determine one of three condition of inherited constitutional jaundice. The study proved that the fuzzy logic technique gives high accuracies in the range of 95% to 100% in the identification of the three aforementioned diseases.

Mansor *et al*. [28] further introduced a colour detection method in the monitoring of newborn jaundice. The study involves three processes in the jaundice detection system. The first stage is the extraction of skin feature information from video recordings of the newborn whereas the second stage involves the selection of quantitative features of unique behavioural characteristics of the newborn. The mean, standard deviation, skewness, kurtosis, energy and

entropy parameters are determined. The third stage was the validation process to distinguish the presence of jaundice. Luminance (Y) and chroma (CbCr) colour spaces are used for jaundice detection from the skin colour. Based on the feature extraction analysis between a jaundiced and non-jaundiced newborn, kurtosis data presented a higher predictive value when compared to the other variables. Thus, this feature has been selected to be used in the screening and monitoring of newborn jaundice as part of the robust image detection tool.

Castro-Ramos *et al*. [29] had developed a similar method to detect newborn jaundice by obtaining the skin digital images of the palm, soles and forehead of the newborns. Images captured are further analysed in terms of the RGB attributes and diffuse reflectance spectra. The computed analysis is further tested by the support vector machine (SVM) to determine the presence of jaundice. The method conferred a sensitivity of 71.8% and the specificity of 78.8% with 20 spectra. Hence, this promising method may be an excellent technique to evaluate between the different levels of bilirubin in the newborn.

Another study using the image processing technique in the detection of neonatal jaundice has been proposed by Aydın *et al*. [30]. This study used the 8-colour calibration card to analyse the captured images. The calibration card had to be disposed after each use and be replaced with a new one prior to each use to avoid the risk of infection in the newborn, hence comes with an added cost. Over time, improvement has been done in the image processing part with the removal of the unnecessary background.

White balancing is used in this study to improve the resolution and sharpness of the captured images. In the machine learning regressions, two algorithms (kNN Regression and Support Vector Regression) are adopted to guide the machine in determining the bilirubin level. The compliance rate between the system and the standard blood test results was 85% using the kNN algorithm, as compared to the compliance rate of 75% when using the SVR algorithm. F-statistical test and ROC analysis in determining the accuracy of the data and the performance of the system showed the excellent success rate of 85%.

3. CONCLUSION

In conclusion, jaundice is a common clinical encounter in neonatal setting and is usually evident in the first week of life. Apart from that, jaundice is also one of the main causes of re-admissions to the hospital in the early postnatal period. Current practices commonly used in the clinical setting for bilirubin measurements are the TSB measurement and the TcB assessment.

Despite the TSB invasive technique, it is the gold standard diagnostic and monitoring method for bilirubin measurement [25]. TcB is a non-invasive measurement method requiring a specialized meter. The spectrum of optical signal reflected from the newborn's subcutaneous tissues is analysed by a specialised meter analyses [3]. This technique differentiates the yellow discoloration on a blanched skin as an estimate of jaundice, as compared to the direct quantification in the TSB method [31]. The TcB technique aimed to reduce the frequency of invasive procedures for bilirubin determination in the clinical setting, which can be distressing to the newborn and the parents.

A technology that is more reliable, safe and accurate in measuring the serum bilirubin in the newborn is possible with the thriving development of electronic gadget and technological advancement. The trend of health sensing through smartphones has received growing attention among the community of researchers as a medium to screen diseases. The existence of Internet of Things (IoT) in the medical field advocates a smart healthcare system in monitoring and tracking individual health status.

It is hoped that in the near future, the development of an accurate and feasibly cost-effective, non-invasive device applying the use of smartphones may be developed as a superior technique to the current, routine, invasive methods in the clinical setting in the management of neonatal jaundice.

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