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Hematocrit Evaluation for Identifying Risk of Cyanotic Nephropathy in Patients with Congenital Cyanotic Heart Disease

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Hematocrit Evaluation for Identifying Risk of Cyanotic Nephropathy in Patients with Congenital Cyanotic Heart Disease

Abstract

**Background:** With modern advances in cardiac care, patients with congenital cyanotic heart disease (CCHD) are living longer. As a result of this, the medical community is recognizing an increasing prevalence of non-cardiac complications in these patients. One of the most common complications is development of cyanotic nephropathy, which in turn leads to polycythemia. Elevated hematocrit levels can be an indicator of this process. Due to increased prevalence and a relative lack of qualified specialists, primary care clinicians are in need of an alternative, inexpensive test to establish these patients’ risk of developing cyanotic nephropathy. Measurement of hematocrit fulfills this need.

**Methods:** An exhaustive search of available medical literature was performed using Medline-Ovid, CINAHL, and Web of Science, using the search terms heart defects, kidney diseases, and hematocrit. Google Scholar was also searched, using the terms congenital cyanotic heart disease, kidney disease, and hematocrit. Included studies were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.

**Results:** A total of 78 studies were screened. The cumulative result of the search gave a total of two studies meeting inclusion criteria: two cross-sectional observational studies demonstrating that elevated hematocrit levels can be a reliable indicator of risk of progression to cyanotic nephropathy in patients with CCHD.

**Conclusion:** Elevated hematocrit levels can be a reliable prognostic indicator of the development of cyanotic nephropathy in patients with CCHD. Hematocrit evaluation is the best resource available to primary care clinicians when evaluating patients with CCHD for the risk of developing cyanotic nephropathy. Current evidence suggests that frequent hematocrit screening could lead to early identification of renal damage. By using hematocrit as an evaluation tool, primary care clinicians can positively impact the quality of life of patients with CCHD. Close monitoring of these patients with appropriate diagnostic studies, such as hematocrit, can also lead to a more manageable distribution of patients with CCHD among the healthcare system between specialists and primary care providers.

**Keywords:** congenital cyanotic heart disease, heart defects, chronic kidney disease, cyanotic nephropathy, hematocrit

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Hematocrit Evaluation for Identifying Risk of Cyanotic Nephropathy in Patients with Congenital Cyanotic Heart Disease

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A Clinical Graduate Project Submitted to the Faculty of the
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Biography

[Redacted for privacy]
Abstract

**Background:** With modern advances in cardiac care, patients with congenital cyanotic heart disease (CCHD) are living longer. As a result of this, the medical community is recognizing an increasing prevalence of non-cardiac complications in these patients. One of the most common complications is development of cyanotic nephropathy, which in turn leads to polycythemia. Elevated hematocrit levels can be an indicator of this process. Due to increased prevalence and a relative lack of qualified specialists, primary care clinicians are in need of an alternative, inexpensive test to establish these patients’ risk of developing cyanotic nephropathy. Measurement of hematocrit fulfills this need.

**Methods:** An exhaustive search of available medical literature was performed using Medline-Ovid, CINAHL, and Web of Science, using the search terms heart defects, kidney diseases, and hematocrit. Google Scholar was also searched, using the terms congenital cyanotic heart disease, kidney disease, and hematocrit. Included studies were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.

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**Keywords:** congenital cyanotic heart disease, heart defects, chronic kidney disease, cyanotic nephropathy, hematocrit
# Hematocrit Evaluation for Identifying Risk of Cyanotic Nephropathy in Patients with Congenital Cyanotic Heart Disease

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List of Abbreviations

CBC       complete blood count
CCHD      Congenital Cyanotic Heart Disease
GFR       Glomerular Filtration Rate
MCH       mean cell hemoglobin
MCHC      mean cell hemoglobin concentration
MCV       mean cell volume
Hematocrit Evaluation for Identifying Risk of Cyanotic Nephropathy in Patients with Congenital Cyanotic Heart Disease

BACKGROUND

Congenital cyanotic heart disease (CCHD) used to be considered a terminal diagnosis given to neonates. However, with modern advances in cardiac care, more of these patients are living into adulthood. As the life expectancy of patients with CCHD continues to grow, the medical community is recognizing an increasing prevalence of non-cardiac complications in these patients. Among these complications are polycythemia and cyanotic nephropathy.

The demographic changes and complications associated with CCHD present many obstacles for clinicians to overcome. Current practice is for the primary care provider to refer patients with CCHD to a pediatric cardiologist. While all patients with CCHD should be under the care of a specialist, this approach could cost the patient valuable time waiting for an appointment with an overbooked specialist. Also, this does not address the gap in care these patients experience once they become adults. Patients with CCHD are at greater risk of non-cardiac complications as they age. There are simply not enough adult CCHD specialists available to meet the increasing patient demand. This leads to an increased patient burden on primary care clinicians.

These patients often require expensive, labor-intensive, and frequent evaluation. Primary care clinicians are in need of an alternative, inexpensive test to establish these patients’ risk of acquiring complications. A simple, routine blood test fulfills this need. Due to the pathophysiologic effects of CCHD on the kidneys, clinicians may be able to use hematocrit levels to earlier detect the development of
cyanotic nephropathy.

CCHD leads to chronic hypoxemia due to cardiac insufficiency. The kidneys respond to this by increasing production of erythropoietin, leading to an increased production of red blood cells (RBC). Elevated hematocrit is a reflection of this increased number of circulating RBCs, and is an early indication of this process. This cascade leads to eventual polycythemia, which results in reduced renal plasma flow and filtration. This decrease in filtration rate, as well as increased creatinine and urate, are classic markers of renal dysfunction. However, these classic indicators of nephropathy occur later in the course of the disease process. Therefore, elevated hematocrit can be a harbinger of cyanotic nephropathy in patients with CCHD. Monitoring hematocrit levels can allow for the early detection necessary to prevent irreversible kidney damage.

METHODS

An exhaustive search was performed using Medline-Ovid, CINAHL, and Web of Science, using the following search terms: heart defects, kidney diseases, and hematocrit. Google Scholar was also searched, using the terms congenital cyanotic heart disease, kidney disease, and hematocrit.

Inclusion criteria were defined as studies that measured hematocrit levels in patients with CCHD who developed cyanotic nephropathy. Studies not meeting these criteria were excluded, as well as studies that were published greater than 20 years ago. Included studies were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.

RESULTS

A total of 78 studies were screened. Medline-Ovid yielded nine results, and two of them met inclusion criteria. No results were found using CINAHL. Web of
Science yielded two results; neither met inclusion criteria. Google Scholar yielded 5890 results. Seventeen of these results were screened, and one study met inclusion criteria; this study was a duplicate that was previously found in the Medline-Ovid search. The citations from relevant studies were also searched. The cumulative result of the search gave a total of two studies. One additional retrospective analysis was found, but was excluded due to a publishing date greater than 20 years old. See Table 1.

**Dittrich et al**

Dittrich et al⁶ is a cross-sectional observational study that evaluated 26 patients with CCHD. Patients ranged in age from 10 to 42 years old, and were both male and female. There was no specification for the male to female ratio of study participants. Using random urine specimens, first morning void urine collections, and timed urine samples, the following values were obtained: total urine protein, transferrin, IgG, albumin, α1-microglobulin, and activity of N-acetyl-β-D-glucosaminidase. Blood samples were drawn within one hour of the start of urine collection and were used to obtain serum creatinine, arterial oxygen saturation, and hematocrit values. These values were compared to established norms and used to calculate GFR.⁶

Of the 26 patients that participated in this study, the median arterial oxygen saturation was 80% and the median hematocrit was 52.7%. Ten of these patients had elevated urinary albumin/creatinine ratio, indicating renal dysfunction. There was a significant relationship \((p<0.05)\) between increased serum hematocrit and urinary protein excretion. Hematocrit was the only positive hematologic marker associated with albuminuria \((p=0.0408)\) when the group was split between those patients with and without albuminuria. When proteinuria and albuminuria were compared to other studied
biomarkers, they were found to be the most sensitive parameters of early glomerular injury.

**Awad et al**

Awad et al⁴ is also a cross-sectional observational study with the objective to find useful biomarkers in identifying cyanotic nephropathy in patients with CCHD. A total of 86 pediatric patients were studied, 72 of which were patients with CCHD. Of the 86 participants, 14 were healthy patients and were used as a control group. The treatment group was further separated into 4 equal groups. Group 1 consisted of 18 patients less than 1 year old. Group 2 also had 18 patients, between 1 and 4 years old. Five to 9 year old patients were placed in Group 3, and greater than or equal to 10 year old patients were placed in Group 4. Groups 3 and 4 also had 18 patients each. This study had particular focus on the effect of palliative cardiac surgery, and therefore constructed an additional group of 10 patients (ranging in age from 1 year to 10 years) who underwent palliative surgery. The male to female ratio was not reported.⁴

Hematocrit level was obtained using the pin-prick method with microcapillary tube centrifugation and oxyhemoglobin saturation was measured via pulse oximetry.⁴ For all groups, a random morning urine sample was used to obtain total urine protein, α1-microglobulin, leucine-aminopeptidase, N-acetyl-β-D-glucosaminidase, and creatinine concentration. However, since these biomarkers are not the focus of this review, they will not be discussed here.

This study also found a significant increase in hematocrit and urinary biomarkers in patients with CCHD as compared to the control group. The P values for all delineated groups were <0.05 when compared with the control group. By dividing the participants into groups according to age, Awad et al⁴ also found a significant correlation between patient age and hematocrit. The percentage of patients with
abnormal hematocrit increased from 11 to 83% from the youngest to the oldest age groups. In the additional palliative surgery group, Awad et al\textsuperscript{4} demonstrated a significant decrease in hematocrit percentage and increase in oxygen saturation after surgery as compared to before. Hematocrit was $51.6\%\pm10.5\%$ before surgery, and dropped to $43.7\%\pm76.4\%$ after surgery, and oxygen saturation rose from $63.9\%\pm5.56\%$ to $92.6\%\pm1.57\%$.\textsuperscript{4}

**DISCUSSION**

When considering the risk of patients with CCHD developing cyanotic nephropathy, both studies\textsuperscript{4,6} included in this systematic review point to two important predisposing factors: the extent of hematocrit elevation and the duration of cyanosis. Both variables appear to play a substantial role in predicting the CCHD patient’s risk of developing cyanotic nephropathy.

Perloff et al\textsuperscript{7} demonstrated that hematocrit levels were 55% to 75% in CCHD patients immediately before death, as compared to the control group with hematocrit levels of 34% to 44%. Dittrich et al\textsuperscript{6} found a statistically significant ($p<0.05$) correlation between elevated hematocrit and urine protein excretion, thus indicating renal dysfunction. In fact, when the group was split in half by the median hematocrit, the patients with higher hematocrit levels showed statistical differences in serum creatinine, urine albumin, and proteinuria.\textsuperscript{6}

This study\textsuperscript{6} went a step further and analyzed other hematologic markers, to determine whether there were additional correlations with evidence of cyanotic nephropathy. RBC count, hemoglobin, mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) were all measured, and none were found to have predictive value of renal cyanotic nephropathy.\textsuperscript{6} This implies that by solely looking at hematocrit levels, a clinician can
accurately predict the patient’s risk of developing this fatal complication of CCHD.

Another study\textsuperscript{3} showed that acute changes in hematocrit are accompanied by acute changes in renal perfusion, which is actually reversible. So with early identification, this process of kidney damage can be reversed. The implications of this are substantial. If an abrupt increase in hematocrit is identified early enough, the early stages of renal damage can be treated, and fulminant renal failure can be prevented.\textsuperscript{7} However, the longer cyanotic nephropathy continues, the increasing likelihood that the resultant renal failure will become chronic. Patients with CCHD could live longer, healthier lives if clinicians would frequently monitor this value.

The other important risk factor in the development of cyanotic nephropathy, is the duration of cyanosis. Duration of cyanosis is directly related to the age of the patient.\textsuperscript{4,6} The longer the CCHD patient is exposed to cyanosis, the greater their risk of developing cyanotic nephropathy. This is confirmed by Krull et al\textsuperscript{8} findings that patients with CCHD develop significant proteinuria and renal dysfunction in the second decade of life. Although Awad et al\textsuperscript{4} only studied children, it was still found that patients developed abnormal lab levels for glomerular function and tubular integrity the longer they were exposed to cyanosis.

Wilcox et al\textsuperscript{3} conducted a study on CCHD patients with polycythemia, which further correlates the relationship of hematocrit to renal damage. This study primarily investigated cor pulmonale as it relates to pulmonary function and CCHD. However, it also commented extensively on the observed elevated hematocrit in these patients (mean of 62\% ± 6\% SD).\textsuperscript{6}

The repeated findings of elevated hematocrit in multiple studies\textsuperscript{3,4,6,7,9} further support the assertion that this measure is a valuable indicator of progression to cyanotic nephropathy. However, despite these extensive and statistically significant findings, there is still debate as to how to address this complication once it has been
identified.

Wilcox et al\textsuperscript{3} attempted to investigate the outcome of hematocrit reduction via therapeutic phlebotomy and replacement with a dextrose solution. The results point to a possibility that GFR could be improved in polycythemic CCHD patients by performing this exchange transfusion in effort to reduce hematocrit levels. However, this was a very small study (7 patients), and is supported by findings in non-human studies.\textsuperscript{3} Clearly, further investigation needs to be done to determine if elimination of erythrocytosis could be safely performed, and if it would be effective in reversing or preventing the incidence of cyanotic nephropathy.

Awad et al\textsuperscript{4} was also able to investigate possible treatment outcomes by studying the effect of palliative surgery on hematocrit levels. Palliative surgery resulted in increased oxyhemoglobin saturation, which in turn led to significantly decreased hematocrit levels and urine markers for impaired renal function. Palliative surgery can decrease the degree of cyanosis, and delay progression to cyanotic nephropathy.\textsuperscript{4}

The implications of elevated hematocrit findings upon medical treatment is still yet to be determined. The uncertainty associated with treatment options for these patients is only one limitation. The studies included in this systematic review have other limitations that should be addressed. For a comprehensive overview of criteria for assessing the overall quality of studies included in this systematic review, please see Table 1.

**Variability**— There was not substantial variability across studies. The Awad et al\textsuperscript{4} study was published 5 years after the Dittrich et al\textsuperscript{6} study and cited the Dittrich et al study frequently. Both studies also cited many identical resources. Other related studies\textsuperscript{3,7,9} showed similar results, linking elevated hematocrit to the incidence of other CCHD related complications (though, these studies were ultimately excluded...
due to failure to answer the clinical question posed in this systematic review). The only exception was Krull et al,\textsuperscript{8} that reported no statistical correlation between proteinuria and hematocrit. However, this study was 25 years old and had a small sample size. Moreover, of the small sample size, a very small number of patients showed any signs of nephropathy at all. The sample was also a very select group, consisting of only patients younger than 25, none of whom had undergone corrective surgery.\textsuperscript{8} This study was ultimately excluded due to the outdated publishing date. Therefore, of the two included studies,\textsuperscript{4,6} there was no variability among results.

**Other limitations**- Both included studies,\textsuperscript{4,6} being cross-sectional in design have an inherent flaw in that they lack longitudinal data. Further studies with serial hematocrit measurements over time and the correlation to degree of renal impairment would be beneficial.

There were also flaws related to sample size. Dittrich et al\textsuperscript{6} had a sample size of only 26 participants, and Awad et al\textsuperscript{4} had a sample size of 86. The small sample size in both studies presented an issue with imprecision. According to Dimopoulos et al,\textsuperscript{10} there is a 9\% prevalence of cyanotic nephropathy in patients with CCHD. However, according to Dittrich et al,\textsuperscript{6} 38\% of their patients showed signs of renal impairment. The study conducted by Dittrich et al\textsuperscript{6} appears to imply that the incidence of cyanotic nephropathy is much higher in patients with CCHD than has been otherwise observed. This discrepancy may have been eliminated, given a larger sample size.

Both studies\textsuperscript{4,6} measured a variety of lab results, one of which was the patients’ hematocrit level. The primary focus was not the identification of variability of hematocrit. It was not measured in retrospect or an incidental finding, so did not pose a serious threat to validity. However, it would have been preferable to see a study where hematocrit levels were the primary focus.
Dittrich et al\textsuperscript{6} had a minor limitation of failure to include a control group. The study was not downgraded under this criterion due to the fact that the study measured a common laboratory value with previously established, widely accepted normal hematocrit ranges.

Awad et al\textsuperscript{4} had more variables that needed refinement. Their sample consisted only of children. Given that the incidence of cyanotic nephropathy increases with age,\textsuperscript{4,6} this created an inadequately representative sample. Awad et al\textsuperscript{4} also failed to provide adequate details regarding the timing of when the blood sample was taken as compared to the urine sample. If the samples were collected at significantly different times, accuracy of the results may have been compromised.

Despite the limitations of these studies, there is highly suggestive evidence that elevated hematocrit is a reliable predictor of cyanotic nephropathy in patients with CCHD. A larger study should be performed in order to definitively confirm the answer to this question. However, the current evidence is already quite convincing and makes physiologic sense. Given these factors, hematocrit evaluation should be a routine test in the primary care clinician’s management of patients with CCHD. The question of importance of performing hematocrit screening should not be the focus of future studies. Future studies should actually focus on frequency of evaluation and should establish defined parameters for which urgent referral and treatment should be done. Perhaps the most pressing and concerning question is treatment. Further studies are severely needed to determine appropriate treatment for these patients.

**CONCLUSION**

While further studies are needed, the lack of variability between current studies and statistical significance of measured variables in these studies cannot be denied. Further research needs be performed to assess treatment options for these
patients, once elevated hematocrit and renal compromise have been identified. There is also no research regarding the use of prophylactic renoprotective therapy, such as ACE inhibitors, for patients with CCHD. Clearly, the lack of specialty care of adult patients with CCHD is a barrier to these studies being conducted. However, one barrier that does not need to exist is early identification of cyanotic nephropathy in the CCHD patient, as primary care clinicians are able to bridge this gap in patient care.

One of the challenges that primary care clinicians face is providing continual follow-up care for patients with complicated chronic medical illnesses. Without specializing in any of these conditions, primary care clinicians need to be able to identify risk factors for complications in these patients and refer them on for more specialized care. It is vitally important for clinicians to be able to use resources that are readily available and affordable to accomplish this. CBC with emphasis on hematocrit value is the best resource available to primary care clinicians when evaluating patients with CCHD for the risk of developing cyanotic nephropathy. Current evidence suggests that frequent hematocrit screening could lead to early identification of renal damage, which is reversible in early stages.6 Using hematocrit as an evaluation tool, primary care clinicians can positively impact the quality of life of patients with CCHD and influence the immediacy of care that these patients receive from specialists.
References


Table 1: Quality Assessment of Reviewed Articles

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*Small sample size