

Evaluation of the correlation between biliary tract dilatation as determined by percutaneous transhepatic cholangiography and serum bilirubin levels in patients with malignant biliary obstruction

Malign biliyer obstrüksiyonu olan hastalarda perkütan transhepatik kolanjiografide saptanan safra yolları dilatasyonu ile serum bilirubin düzeyleri arasındaki ilişkinin değerlendirilmesi

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Background and Aims: The aim of this study was to investigate a possible correlation between biliary tract dilatation as measured via percutaneous transhepatic cholangiography and the plasma bilirubin levels in patients diagnosed with icteric obstruction due to malignant causes.

Materials and Methods: The study covered 299 patients diagnosed and discharged for icteric obstruction due to malignant causes and who underwent percutaneous transhepatic cholangiography between April 2006 and April 2010. Measurements were taken in the proximity of biliary narrowness/obstruction, at the widest site of the dilated biliary tracts in patients who underwent percutaneous transhepatic cholangiography. The results of the measurements were calculated in millimeters via the calibration of catheters through the images. The biochemically determined plasma total bilirubin values of patients were studied 1 day before the percutaneous transhepatic cholangiography examination or within the same day but prior to the examination. The patients were divided into subgroups as aggregate or according to age, pathologic diagnosis, gender, and Bismuth classification prior to the investigation of the bilirubin and biliary tract correlation. **Results:** Examination of the patients in aggregate without any classification or by dividing the patients into subgroups according to age, pathologic diagnosis, gender, and Bismuth classification did not reveal a significant correlation between the diameter of the biliary tract and serum total bilirubin levels. **Conclusions:** Since there was no significant correlation between the serum total biliary level and biliary tract dilatation in malignant biliary obstruction, the serum total bilirubin levels become prominent, while the biliary tract dilatation becomes of secondary importance in assessment of a patient via the invasive practice through percutaneous transhepatic cholangiography.

Key words: Malignant biliary obstruction, percutaneous transhepatic cholangiography, bile duct dilatation, serum bilirubin levels

Giriş ve Amaç: Bu çalışmanın amacı, malign nedenlere bağlı tıkanma ikteri tanısı olarak perkütan transhepatik kolanjiografi yapılan hastalarda, safra yollarındaki dilatasyonun perkütan transhepatik kolanjiografi aracılığıyla saptanan ölçüm değeri ile plazma bilirubin değerleri arasında ilişki olup olmadığını araştırmaktır. **Gereç ve Yöntem:** Çalışmaya Nisan 2006–Nisan 2010 tarihleri arasında, malign nedenlere bağlı tıkanma ikteri tanısı olarak gönderilen ve perkütan transhepatik kolanjiografi yapılan 299 hasta dahil edildi. Tıkanma sarılığı 201 hastada periampuller bölgenin primer tümörlerine bağlı olarak gelişmekteydi. 98 hastada ise sarılık, mide kansinomu, kolon kanseri, Non-Hodgkin lenfoma, meme kanseri, özefagus kanseri ve retroperitoneal malign neoplazinin metastatik lezyonlarının neden olduğu darlık/tıkanıklık sonucu gelişmekteydi. Perkütan transhepatik kolanjiografi işlemi yapılan hastalarda safra yollarında darlık/tıkanıklık seviyesinin proksimalinde, dilate safra yollarının en geniş yerinde ölçümler yapıldı. Kullanılan kateterlerin görüntü üzerinden kalibrasyonu vasıtasıyla, yapılan ölçümlerin milimetre cinsinden değeri hesaplandı. Hastaların biyokimyasal olarak plazma total bilirubin değerleri, perkütan transhepatik kolanjiografi incelemesinden 1 gün önce veya aynı gün işlem öncesinde çalışıldı. Hastalar bütün olarak ve yaş, patolojik tanı, cinsiyet ve Bismuth klasifikasyonuna göre subgruplara ayrılarak bilirubin ve safra yolu çapı korelasyonu araştırıldı. **Bulgular:** Hastalar bütün olarak bir sınıflama yapılmadan ele alındığında veya yaş, patolojik tanı, cinsiyet ve Bismuth klasifikasyonuna göre subgruplara ayrılarak incelendiğinde, perkütan transhepatik kolanjiografi aracılığıyla ölçülen safra yolları çapı ile serum total bilirubin düzeyleri arasında anlamlı korelasyon saptanmadı. **Sonuç:** Malign biliyer obstrüksiyonda; serum total bilirubin düzeyi ile safra yolu dilatasyonu arasında korelasyon saptanmadığından, perkütan transhepatik kolanjiografi aracılığıyla yapılan girişimsel işlemler ile hastaların değerlendirilmesinde, karaciğer fizyopatolojisi de göz önüne alındığında, serum total bilirubin düzeyleri ön plana çıkmakta, safra yolu dilatasyonu ise ikinci planda kalmaktadır.

Anahtar Kelimeler: Malign biliyer tıkanıklık, perkütan transhepatik kolanjiografi, safra yolu dilatasyonu, serum bilirubin düzeyleri

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INTRODUCTION

Obstructive biliary tract diseases are commonly encountered in daily practice, often causing complaints such as jaundice, right upper quadrant pain, nausea, vomiting, and fever, most commonly triggered by calculus, inflammation and tumor, which must be treated by carefully and quickly identifying the cause (1,2).

Today, ultrasonography (USG) and computerized tomography (CT) are the primary choices in imaging for diagnosing obstructive biliary tract diseases due to their high diagnostic accuracy and ease of use, while magnetic resonance cholangiopancreatography (MRCP) is preferred as it is non-invasive and does not contain ionizing radiation. These examinations may identify the enlarged biliary tracts and reveal the reason for and degree of the obstruction, but they may be insufficient for identifying small lesions and partial obstructions or to examine peripheral biliary tracts with normal diameter. Thus, they fail to provide any forms of treatment other than their diagnostic role (3-5).

Percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) are invasive methods that are still considered gold standards in the diagnosis of obstructive biliary tract diseases, as they allow the imaging of the general biliary system anatomy as well as anomalies including peripheral small biliary tracts. They are also utilized for medical intervention for biliary tract pathologies through advanced invasive radiological methods and for treatment-palliation purposes, but they require experienced operators in practice (6,7).

Biliary tract dilatation is an expected outcome in the proximity of narrowness/obstruction in the case of obstruction-caused jaundice. In the practice of diagnostic modalities, dilatation is mentioned, but without an indication of a measurable value of dilatation. There is currently no agreement on whether or not there is a correlation between biliary tract dilatation and serum bilirubin levels, and there is no confirmed data on which would be more effective in observing the response to treatment. In this study, we aimed to demonstrate the correlation between the serum total bilirubin values and dilatation as determined by millimetric measurements at the widest site in the proximity of narrowness/obstruction using PTC in patients diagnosed with icteric obstruction due to laboratory and clinically malignant reasons.

MATERIALS and METHODS

The study covered 299 patients (97 females, 202 males;

age range: 20-87 years, mean age: 60), diagnosed using biochemical and radiological methods and discharged for icteric obstruction due to malignant causes, who underwent PTC in the radiology ward between April 2006 and April 2010. Approval for the study was attained from the Training Planning Coordination Board.

Obstructive jaundice was associated with malignant causes in all patients, and in 201 patients, it developed due to narrowness/obstruction caused by primary tumors in the periampullary region (Figures 1, 2). In 98 patients, the jaundice developed due to narrowness/obstruction caused by metastatic lesions of stomach carcinoma (Ca), colon Ca, non-Hodgkin lymphoma, breast Ca, esophageal Ca (Figure 3), and retroperitoneal malignant neoplasia. Table 1 shows the causes of obstructions in our cases.

Monoplane digital subtraction angiography (DSA) device (Philips Integris Allura, Holland) was used for the procedure. The PTC procedure was performed by inserting the 21-gauge Chiba needle, accompanied by fluoroscopy, into the biliary tracts with approach from the midaxillary line on the right and subxiphoid on the left. An 18-gauge Chiba needle was used for selective biliary tract cannulation, and the catheter was placed. Following sufficient intra- and extrahepatic biliary tract opacification, images were captured by angling in anteroposterior, cranio-

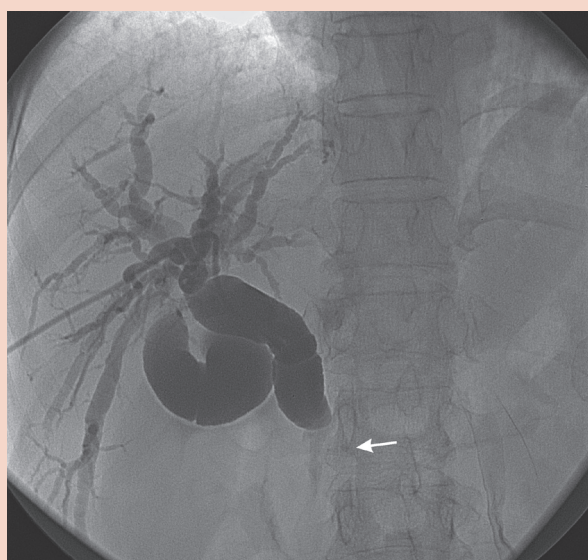


Figure 1. Male patient aged 67 with pancreatic Ca. Mass caused complete obstruction at the distal end of choledoch (arrow); instant termination in choledoch caused prevalent dilatation in intra- and extrahepatic biliary tracts (Bismuth type 1). Largest diameter of biliary tracts measured in the proximity of narrowness was 20 mm, and plasma total bilirubin value prior to the procedure was 4,9 mg/dl.

caudal and oblique aspects. Calibration was performed through the catheter using these images. Measurements were performed at the widest site of the dilated biliary

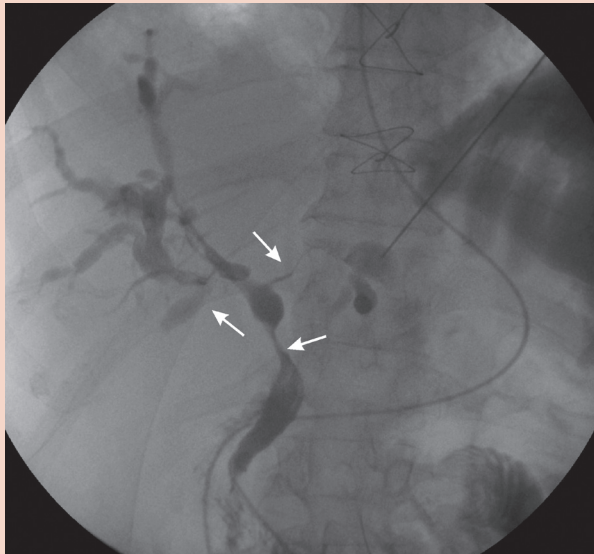


Figure 2. Male patient aged 65 with gallbladder Ca. Mass showed bilateral and multicentric spread, causing narrowed areas in intra- and extrahepatic biliary tracts (Bismuth type 4). Largest diameter of biliary tracts measured in the proximity of narrowness was 15 mm, and plasma total bilirubin value prior to the procedure was 45,1 mg/dl.



Figure 3. Male patient aged 62 with primary esophageal Ca. Mass caused advanced narrowness and prevalent dilatation in intrahepatic biliary tracts at the hilar intersection in the bifurcation localization of the main right and left hepatic biliary tracts (Bismuth type 2). Largest diameter of biliary tracts measured in the proximity of narrowness was 22 mm, and plasma total bilirubin value prior to the procedure was 8,9 mg/dl.

tracts in the proximity of the biliary tract narrowness/obstruction. The measured value was calculated in millimeters. The biochemically determined plasma total bilirubin values of patients were studied one day before the PTC examination or within the same day but prior to the examination.

All biological and radiological parameters were recorded in the computer using the Statistical Package for the Social Sciences (SPSS) for Windows 15.0 media. The correlations between the diameters measured at the widest site of the biliary tracts in the proximity of the narrowness/obstruction and serum bilirubin levels were investigated using non-parametric correlation test. Degree for r value was assessed as 0 - 0,2: weak correlation, 0,2-0,5: medium correlation, 0,5-0,8 strong correlation, and r=0,8-1: perfect correlation. A value of $p < 0,05$ was considered statistically significant in all tests.

RESULTS

The average widest diameter measured in the proximity of biliary tract narrowness/obstruction was 17,13 ($\pm 6,07$) mm in all patients. The average total bilirubin level for all patients was 15.98 ($\pm 9,76$) mg/dl. When assessing the patients as a whole without any classification, no significant correlation was found between the biliary tract diameter and serum total bilirubin level (Figure 4, Table 2, $r=0,002$, $p=0,973$).

In male patients, the average widest diameter measured in the proximity of biliary tract narrowness/obstruction was 17,58 ($\pm 5,90$) mm, and the average total bilirubin level was 16,04 ($\pm 10,27$) mg/dl. In male patients, no significant correlation was found between the biliary

Table 1. Causes of obstructive jaundice

Diagnosis	Number of Cases
Stomach Ca met	84
Cholangiocarcinoma	79
Pancreas Ca	66
Gallbladder Ca	29
Oddi Tm	21
Colon Ca met	9
Hepatoma	5
Non-Hodgkin lymphoma met	2
Ampulla of Vater Ca	1
Breast Ca met	1
Esophagus Ca met	1
Retroperitoneal malignant neoplasia met	1
TOTAL	299

Met: metastasis, Ca: carcinoma, Tm: tumour

tract diameter and serum total bilirubin level (Table 2, $r=0,004$, $p=0,953$).

In female patients, the average widest diameter measured in the proximity of biliary tract narrowness/obstruction was $16,21 (\pm 6,35)$ mm, and the average total bilirubin level was $15,86 (\pm 8,67)$ mg/dl. In female patients, no significant correlation was found between the biliary tract diameter and serum total bilirubin level (Table 2, $r=0,023$, $p=0,825$).

For patients with metastatic Ca, the average widest di-

ameter measured in the proximity of biliary tract narrowness/obstruction was $16,97 (\pm 5,98)$ mm, and the average total bilirubin level was $15,11 (\pm 11,09)$ mg/dl. In patients with metastatic Ca, no significant correlation was found between the biliary tract diameter and serum total bilirubin level (Table 2, $r=0,099$, $p=0,328$).

For patients with primary Ca, the average widest diameter measured in the proximity of biliary tract narrowness/obstruction was $17,22 (\pm 6,13)$ mm, and the average total bilirubin level was $16,42 (\pm 9,04)$ mg/dl. In patients with primary Ca, no significant correlation was found between the biliary tract diameter and serum total bilirubin level (Table 2, $r=0,076$, $p=0,287$).

In patients classified as cholangiocarcinoma, pancreatic Ca, gallbladder Ca, Oddi tumor, and hepatoma, no significant correlation was found between the serum total bilirubin level and biliary tract diameter (Table 2).

In patients classified as group 1, 2, 3a, 3b, and 4 according to Bismuth classification, no significant correlation was found between the serum total bilirubin level and biliary tract diameter (Table 2).

In age classification as 2nd – 3rd decade, 3rd – 4th decade and over 4 decades, no significant correlation was found between the serum total bilirubin level and biliary tract diameter (Table 2).

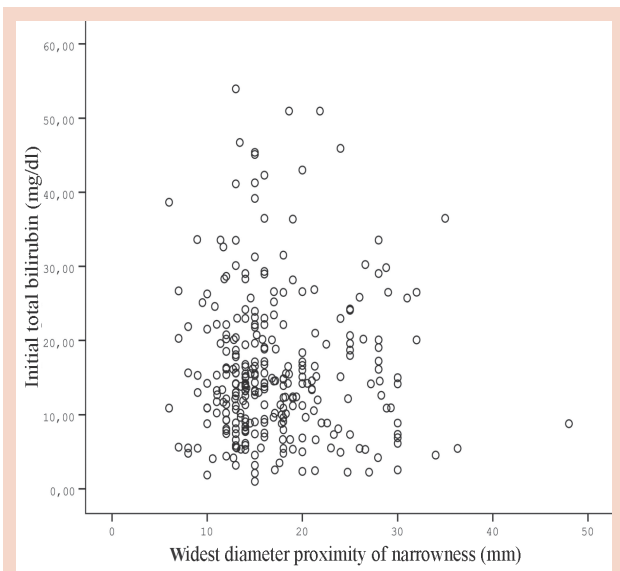


Figure 4. Variation in the correlation between total bilirubin level and biliary tract width in all patients.

DISCUSSION

A normal person produces approximately 4 mg/kg bilirubin daily. A large portion of this is created through the

Table 2. The correlation between serum total bilirubin values and biliary tract diameter

Serum Total Bilirubin – Biliary Tract Width Correlation	r	P
All patients (n=299)	0,002	0,973
Male patients (n=202)	0,004	0,953
Female patients (n=97)	0,023	0,825
Patients with metastatic Ca (n=98)	0,099	0,328
Patients with primary Ca (n=201)	0,076	0,287
Patients with cholangiocarcinoma (n=79)	0,084	0,463
Patients with pancreatic Ca (n=66)	0,304	0,013
Patients with gallbladder Ca (n=29)	0,280	0,141
Patients with Oddi Tm (n=21)	0,201	0,383
Patients with hepatoma (n=5)	0,000	1,000
Patients in Bismuth group 1 (n=167)	0,070	0,373
Patients in Bismuth group 2 (n=84)	0,001	0,993
Patients in Bismuth group 3A (n=28)	0,303	0,117
Patients in Bismuth group 3B (n=12)	0,416	0,179
Patients in Bismuth group 4 (n=9)	0,084	0,831
Patients aged 20-29 (n=7)	0,048	0,911
Patients aged 30-39 (n=7)	0,286	0,493
Patients aged 40 and over (n=285)	0,010	0,867

Ca: carcinoma, Tm: tumour

catabolism of hemoglobin heme group. In the case of obstructive jaundice, plasma bilirubin amounts rise consistently and reach a plateau phase of 10-30 mg/dl if completely obstructed (8,9).

The pressure at which bile is excreted from the liver ranges between 120-250 mm H₂O. This pressure ensures normal movement of bile flow. The pressure in extrahepatic biliary tracts must be lower than the pressure in intrahepatic biliary tracts to enable bile flow, which is normally 100-150 mm H₂O. In the case of extrahepatic biliary tract pressure of over 300 mm H₂O, the bile excretion from the liver is inhibited. Increasing the biliary pressure causes dilatation in extra- and intrahepatic biliary tracts (10,11).

The first alterations in long periods of biliary tract obstruction emerge at the bile canaliculi. Canaliculi enlarge during cholestasis, and swelling and deformation emerges in the microvilli. If the cholestasis expands any further, elongation and inflection in addition to significant proliferation emerge at the canaliculi; the resultant bile reabsorption triggers an inflammatory reaction with polymorphonuclear cellular infiltration to the portal paths. This is a tissue reaction to an irritant chemical stimulus in which the cholangiolitic alterations are followed by fibrosis. Due to the toxic effect of bilirubin and bile acids accumulated in hepatocytes in periportal areas, the reticulum is ruptured and canaliculus membrane components are solubilized. In this period, the canalicular alkaline phosphatase can be found in the blood circulation with increasing levels. These alterations are quickly reversed if the obstruction is remedied within two weeks. If the obstruction persists, the reticulin precipitating in periportal areas mutates as type-1 collagens, developing scar fibrosis in the vicinity of biliary canals. Further progression of intrahepatic fibrotic alterations mechanically obstructs the sinusoidal current, causing secondary portal hypertension. Due to the lobular structure of the liver, this fibrotic process rarely causes biliary cirrhosis, and the fibrotic alterations tend to reverse if the obstruction is remedied (12-14).

While surgery is the primary method of choice for palliative and curative treatment in obstructive jaundice, endoscopic and transhepatic approaches are also practiced. Particularly with a palliative modality, in the case of endoscopic and transhepatic drainage (external-internal stent, etc.), the patient's examination is performed by monitoring serum bilirubin levels and biliary tract dilatation (15).

Previous studies have explored the correlation between bilirubin levels and biliary tract dilatation in biliary obstruction. The results of such studies have been inconsistent. In a study conducted on 23 patients with extrahepatic

biliary tract obstruction, Lapis *et al.* found a positive correlation ($r=0,75$) between serum total bilirubin levels and the choledoch diameter measured via contrast cholangiographic examination (16).

Ketelsen *et al.* conducted a prospective examination on 52 patients who received hematological stem cell transplantation, using the abdominal CT method. Twenty-seven of the patients developed graft-versus-host disease, while the 25 patients that did not develop complications constituted the control group. In the patients that developed graft-versus-host disease, thickening of the duodenal wall caused narrowness/obstruction in the distal section of the choledoch, leading to biliary tract dilatation in the proximity of this level. The study measured the diameter at the widest site of the dilated choledoch using abdominal CT in the proximity of the narrowness/obstruction, and found that the measured diameter was correlated with the cholestatic enzymes and serum bilirubin levels; they also found a positive correlation ($r=0,421$) between the serum bilirubin level and choledoch diameter (17).

A retrospective study conducted by Karvonen *et al.* on 212 patients with extrahepatic biliary tract obstruction reported that, according to receiver operating characteristics (ROC) analysis, the plasma bilirubin level is significant in malignant-benign (calculus) distinction of the underlying disease, while the biliary tract dilatation levels were not significant in malignant-benign (calculus) distinction of the underlying disease (with measurements taken at the widest site of the dilated biliary tracts) (18).

In the study of Pedersen *et al.*, they conducted sonographic examination in a total of 176 icteric patients (113 obstructive, 63 non-obstructive) who had a definitive diagnosis through surgery, autopsy or ERCP, and they investigated the diagnostic value of sonography and of variations in the serum bilirubin values. In biliary tract obstructions associated with malignant causes, the sonography found one or more biliary tracts instantly terminated and the serum bilirubin values reached greater peak levels compared to obstructions associated with benign causes (calculus). However, their study reported that the increase in serum bilirubin level is not well-correlated with the level of biliary tract dilatation (19).

The study conducted by Staritz *et al.* on 57 patients with extrahepatic biliary tract obstruction using endoscopic manometry via ERCP indicated that there was no correlation between the choledoch diameter and intraluminal pressure measurements (20).

Our study was conducted using PTC, an expensive and demanding imaging method, during which the patient

and personnel are exposed to radiation. There is also the risk of infection for the patient, as PTC is an invasive method. Our study covers patients with biliary tract narrowness associated with malignant causes; patients with biliary tract narrowness associated with benign causes were not included.

During the process, the contrast agent was administered until the distal biliary tracts were filled with opaque material, and all procedures were performed by the same team. For the purpose of imaging the dilated biliary tracts, the minimal dilatation associated with opaque agent administration during PTC was disregarded. This may be considered a limitation of this study.

In our study, when the patients were assessed in whole without any classification, no correlation was found between the serum total bilirubin levels and biliary tract dilatation. Patients categorized in groups 1, 2, 3a, 3b, and 4 according to Bismuth classification were assessed as part of the respective groups, which also revealed no correlation between the biliary tract dilatation and serum bilirubin levels. Classifying the patients according to primary and metastatic masses or according to age as 2nd

– 3rd decade, 3rd – 4th decade and over 4 decades, the individual evaluation of each group revealed no significant correlation between the measured biliary tract diameter and serum bilirubin levels. Consequently, our study found no correlation between the serum total bilirubin level and biliary tract dilatation in patient groups with biliary obstruction associated with malignant causes; therefore, serum total bilirubin levels come to prominence in the evaluation of patients with malignant biliary obstruction, considering also the liver physiopathology, while the biliary tract dilatation remains of secondary importance.

For the patient group covered by the study, if surgical methods fail to provide an effective benefit, it is recommended to perform outpatient observation and treatment after measuring the bilirubin levels, without waiting for the decrease in dilatation of the biliary tracts if the biliary drainage is conducted via PTC. It may thus be suggested that the patient's hospitalization time will decrease, and the patient will be protected from hospital-borne infections. It is also known that avoiding unnecessary PTC would reduce the dosage of radiation as well as the risk of infection to the patient due to the procedure's invasive nature.

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