Chapter4

Precision of Prediction in the Simple Calibration Model

4.1 Introduction:

In this chapter the precision of the prediction of the out come of the standard treatment X from the nonstandard treatment Y, as reflected in the degree of confidence on the predicted value $\hat{X}$ is investigated. The investigation covered different sample sizes, different degrees of linear correlation between X and Y as well as different population variances.

A Monte carlo experiment, using a computer programme written by the researcher, is employed.

4.2Jaundice disease:

Jaundice, also known as icterus, is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes caused by high blood bilirubin levels. This hyperbilirubinemia causes increased levels of bilirubin in the extracellular fluid. Concentration of bilirubin in blood plasma is normally below 1.2 mg/dL (under 25 µmol/L). A concentration higher than approximately 3 mg/dL (over 50 µmol/L) leads to jaundice. The term jaundice is from the French word jaunisse, meaning "yellowish".

Jaundice is often seen in liver disease such as hepatitis or liver cancer. It may also indicate leptospirosis or obstruction of the biliary tract, for example by gallstones or pancreatic cancer, or less commonly be congenital in origin (e.g., biliary atresia). Jaundice in newborns is common and in most cases it is not a problem. It is often the result of a normal, temporary physiologic state. But sometimes it is severe and with very high levels of bilirubinemia being toxic to the brain.

Yellow discoloration of the skin, especially on the palms and the soles, but not of the sclera and mucous membranes (i.e., oral cavity) is due to carotenemia—a harmless condition important to differentiate from jaundice. Other things that can cause similar discoloration include as a side effect to the use of drug mepacrine and excessive exposure to phenols.

4.2.1Signs and symptoms:

The main symptom of jaundice is a yellowish discoloration of the white area of the eye and the skin. Urine is dark in colour. Slight increases in serum bilirubin are best detected by examining the sclerae, which have a particular affinity for bilirubin due to their high elastin content. The presence of scleral icterus indicates a serum bilirubin of at least 3 mg/dL. The conjunctiva of the eye are one of the first tissues to change color as bilirubin levels rise in jaundice. This is sometimes referred to as scleral icterus. However, the sclera themselves are not "icteric" (stained with bile pigment) but rather the conjunctival membranes that overlie them. The yellowing of the "white of the eye" is thus more properly termed conjunctival icterus. The term "icterus" itself is sometimes incorrectly used to refer to jaundice that is noted in the sclera of the eyes, however its more common and more correct meaning is entirely synonymous with jaundice.

4.2.3Complications:

Hyperbilirubinemia, more precisely hyperbilirubinemia due to the unconjugated fraction, may cause bilirubin to accumulate in the gray matter of the central nervous system, potentially causing irreversible neurological damage leading to a condition known as kernicterus. Depending on the level of exposure, the effects range from clinically unnoticeable to severe brain damage and even death. Newborns are especially vulnerable to hyperbilirubinemia-induced neurological damage and therefore must be carefully monitored for alterations in their serum bilirubin levels.

4.2.4 Differential diagnosis:

Types of jaundice:

When a pathological process interferes with the normal functioning of the metabolism and excretion of bilirubin just described, jaundice may be the result. Jaundice is classified into three categories, depending on which part of the physiological mechanism the pathology affects. The three categories are:

4.2.41Pre-hepatic:

Pre-hepaticular jaundice is caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells). Unconjugated bilirubin comes from the breakdown of the heme pigment found in red blood cells'

hemoglobin. The increased breakdown of red blood cells leads to an increase in the amount of unconjugated bilirubin present in the blood and deposition of this unconjugated bilirubin into various tissues can lead to a jaundiced appearance. In tropical countries, severe malaria can cause jaundice in this manner. Certain genetic diseases, such as sickle cell anemia, spherocytosis, thalassemia, pyruvate kinase deficiency, and glucose 6-phosphate dehydrogenase deficiency can lead to increased red cell lysis and therefore hemolytic jaundice. Commonly, diseases of the kidney, such as hemolytic uremic syndrome, can also lead to coloration. Defects in bilirubin metabolism also leads to jaundice, as in Gilbert's syndrome (a genetic disorder of bilirubin metabolism which can result in mild jaundice, which is found in about 5% of the population) and Crigler-Najjar syndrome, Type I and II.

In jaundice secondary to hemolysis, the increased production of bilirubin leads to the increased production of urine-urobilinogen. Bilirubin is not usually found in the urine because unconjugated bilirubin is not water-soluble, so, the combination of increased urine-urobilinogen with no bilirubin (since, unconjugated) in urine is suggestive of hemolytic jaundice.

Laboratory findings include:

- Urine: no bilirubin present, urobilinogen > 2 units (i.e., hemolytic anemia causes increased heme metabolism; exception: infants where gut flora has not developed).
- Serum: increased unconjugated bilirubin.
- Kernicterus is associated with increased unconjugated bilirubin; neonates are especially vulnerable to this due to increased permeability of the blood brain barrier.

4.2.4.2Hepatocellular:

- Hepatocellular (hepatic) jaundice can be caused by acute or chronic hepatitis, hepatotoxicity, cirrhosis, drug-induced hepatitis and alcoholic liver disease. Cell necrosis reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup of unconjugated bilirubin in the blood. Other causes include primary biliary cirrhosis leading to an increase in plasma conjugated bilirubin because there is impairment of excretion of conjugated bilirubin into the bile. The blood contains an abnormally raised amount of conjugated bilirubin and bile salts which are excreted in the urine. Jaundice seen in the newborn, known as neonatal

jaundice, is common in newborns as hepatic machinery for the conjugation and excretion of bilirubin does not fully mature until approximately two weeks of age. Rat fever (leptospirosis) can also cause hepatic jaundice. In hepatic jaundice, there is invariably cholestasis.

- Laboratory findings depend on the cause of jaundice.
- Urine: Conjugated bilirubin present, urobilirubin > 2 units but variable (except in children). Kernicterus is a condition not associated with increased conjugated bilirubin.
- Plasma protein show characteristic changes.
- Plasma albumin level is low but plasma globulins are raised due to an increased formation of antibodies.
- Bilirubin transport across the hepatocyte may be impaired at any point between the uptake of unconjugated bilirubin into the cell and transport of conjugated bilirubin into biliary canaliculi. In addition, swelling of cells and oedema due to inflammation cause mechanical obstruction of intrahepatic biliary tree. Hence in hepatocellular jaundice, concentration of both unconjugated and conjugated bilirubin rises in the blood. In hepatocellular disease, there is usually interference in all major steps of bilirubin metabolism—uptake, conjugation and excretion. However, excretion is the rate-limiting step, and usually impaired to the greatest extent. As a result, conjugated hyperbilirubinaemia predominates.
- The unconjugated bilirubin still enters the liver cells and becomes conjugated in the usual way. This conjugated bilirubin is then returned to the blood, probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver. Thus, most of the bilirubin in the plasma becomes the conjugated type rather than the unconjugated type, and this conjugated bilirubin which did not go to intestine to become urobilinogen gives the urine the dark color.

4.2.4.3Post-hepatic:

Post-hepatic jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile containing conjugated bilirubin in the biliary system. The most common causes are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" can live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, cholangiocarcinoma, pancreatitis,

cholestasis of pregnancy, and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome.

In complete obstruction of the bile duct, no urobilinogen is found in the urine, since bilirubin has no access to the intestine and it is in the intestine that bilirubin gets converted to urobilinogen to be later released into the general circulation. In this case, presence of bilirubin (conjugated) in the urine without urine-urobilinogen suggests obstructive jaundice, either intra-hepatic or post-hepatic.

The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments. However, although pale stools and dark urine are a feature of biliary obstruction, they can occur in many intra-hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstruction from hepatic causes of jaundice.

Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus" because of the deposition of bile salts.

No single test can differentiate between various classifications of jaundice. A combination of liver function tests is essential to arrive at a diagnosis.

4.2.5Neonatal jaundice:

Neonatal jaundice is usually harmless: this condition is often seen in infants around the second day after birth, lasting until day 8 in normal births, or to around day 14 in premature births. Typical causes for neonatal jaundice include normal physiologic jaundice, jaundice due to formula supplementation, and hemolytic disorders that include hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, ABO/Rh blood type autoantibodies, or infantile pyknocytosis. Serum bilirubin normally drops to a low level without any intervention required. In cases where bilirubin rises higher, a brain-damaging condition known as kernicterus can occur, leading to significant disability. This condition has been rising in recent years due to less time spent outdoors. A Bili light is often the tool used for early treatment, which often consists of exposing the baby to intensive phototherapy. Sunbathing is effective treatment, and has the advantage of ultra-violet-B, which promotes Vitamin D production. Bilirubin count is lowered through bowel movements and urination, so frequent and effective feedings are especially important

4.2.5Pathophysiology:

Jaundice itself is not a disease, but rather a sign of one of many possible underlying pathological processes that occur at some point along .the normal physiological pathway of the metabolism of bilirubin in blood

When red blood cells have completed their life span of approximately 120 days, or when they are damaged, their membranes become fragile and prone to rupture. As each red blood cell traverses through the reticuloendothelial system, its cell membrane ruptures when its membrane is fragile enough to allow this. Cellular contents, including hemoglobin, are subsequently released into the blood. The hemoglobin is phagocytosed by macrophages, and split into its heme and globin portions. The globin portion, a protein, is degraded into amino acids and plays no role in jaundice. Two reactions then take place with the heme molecule. The first oxidation reaction is catalyzed by the microsomal enzyme heme oxygenase and results in biliverdin (green color pigment), iron and carbon monoxide. The next step is the reduction of biliverdin to a yellow color tetrapyrol pigment called bilirubin by cytosolic enzyme biliverdin reductase. This bilirubin is "unconjugated," "free" or "indirect" bilirubin. Approximately 4 mg of bilirubin per kg of blood is produced each day. The majority of this bilirubin comes from the breakdown of heme from expired red blood cells in the process just described. However approximately 20 percent comes from other heme sources, including ineffective erythropoiesis, and the breakdown of other heme-containing proteins, such as muscle myoglobin and cytochromes

4.2.6 Diagnostic approach:

Most patients presenting with jaundice will have various predictable patterns of liver panel abnormalities, though significant variation does exist. The typical liver panel will include blood levels of enzymes found primarily from the liver, such as the aminotransferases (ALT, AST), and alkaline phosphatase (ALP); bilirubin (which causes the jaundice); and protein levels, specifically, total protein and albumin. Other primary lab tests for liver function include gamma glutamyl transpeptidase (GGT) .(and prothrombin time)

Some bone and heart disorders can lead to an increase in ALP and the aminotransferases, so the first step in differentiating these from liver problems is to compare the levels of GGT, which will only be elevated in liver-specific conditions. The second step is distinguishing from biliary (cholestatic) or liver (hepatic) causes of jaundice and altered laboratory results. The former typically indicates a surgical response, while the latter typically leans toward a medical response. ALP and GGT levels will typically rise with one pattern while aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rise in a separate pattern. If the ALP (10–45 IU/L) and GGT (18–85) levels rise proportionately about as high as the AST (12–38 IU/L) and ALT (10–45 IU/L) levels, this indicates a cholestatic problem. On the other hand, if the AST and ALT rise is significantly higher than the ALP and GGT rise, this indicates an hepatic problem. Finally, distinguishing between hepatic causes of jaundice, comparing levels of AST and ALT can prove useful. AST levels will typically be higher than ALT. This remains the case in most hepatic disorders except for hepatitis (viral or hepatotoxic). Alcoholic liver damage may see fairly normal ALT levels, with AST 10x higher than ALT. On the other hand, if ALT is higher than AST, this is indicative of hepatitis. Levels of ALT and AST are not well correlated to the extent of liver damage, although rapid drops in these levels from very high levels can indicate severe necrosis. Low levels of albumin tend to indicate a .chronic condition, while it is normal in hepatitis and cholestasis

Lab results for liver panels are frequently compared by the magnitude of their differences, not the pure number, as well as by their ratios. The AST:ALT ratio can be a good indicator of whether the disorder is alcoholic liver damage (above 10), some other form of liver damage (above 1), or hepatitis (less than 1). Bilirubin levels greater than 10x normal could indicate neoplastic or intrahepatic cholestasis. Levels lower than this tend to indicate hepatocellular causes. AST levels greater than 15x tends to indicate acute hepatocellular damage. Less than this tend to indicate obstructive causes. ALP levels greater than 5x normal tend to indicate obstruction, while levels greater than 10x normal can indicate drug (toxic) induced cholestatic hepatitis or Cytomegalovirus. Both of these conditions can also have ALT and AST greater than 20× normal. GGT levels greater than 10x normal typically indicate cholestasis. Levels 5–10× tend to indicate viral hepatitis. Levels less than 5× normal tend to

indicate drug toxicity. Acute hepatitis will typically have ALT and AST levels rising 20–30× normal (above 1000), and may remain significantly elevated for several weeks. Acetaminophen toxicity can result in ALT .and AST levels greater than 50x normal

4.3 A Monte carlo experiment:

The experiment consisted of first determining 20 observation of a standard treatment X .The observations actually used were the exact percentages of the bilirubin in the blood of Jaundice patients and were as follows :

6.3, 10, 3.5, 12.5, 20, 17.2, 18.3, 5.8, 9.3, 13, 11.7, 8.9, 22.3, 10.4, 23, 4.3 ,7.5, 8, 19 and 5.

The next step was to decide on "true" values for the regression parameters β_0 and β_1 as well as the error variance σ^2. Based on some studies values for β_0 are chosen as 1.22, 3.75 and 5.79 and the corresponding values for β_1 0 .001, 0 .02, and 0.999.

The population variances used are 3.4, 15.3 and 2.22. This provides three levels(small, medium and large) for each of the parameters β_0 and β_1 and σ^2.

Finally using Eisenhart's simple calibration model:

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i \qquad \text{i} = 1,2,3,...,\text{n}$$

The correspond values for the "nonstandard treatment" Y are generated for each pair (β_0 , β_1) with ε_i drown from normal distribution. This yielded a bivariate population for the bivariate variable (X , Y).The process of generation the population is explained in the next section.

4.4Generation of the population of (X , Y):

The following steps are followed:

d1-Select a value 1.22 *for* β_0 & 0.001 for β_1 and a given value of X say X_1 and define:

$$Y' = \beta_0 + \beta_1 X_1$$

2-From the normal distribution with mean zero and variance $\sigma^2 = 3.4$ select a random number ε and obtain a value of Y as:

$$Y = \beta_0 + \beta_1 X_1 + \varepsilon$$

3-Repeat step(2) 500 times. This yields 500 values of Y corresponding to X_1.

4- Repeat step $(1) \rightarrow (3)$ for other values of X.

5- Repeat step $(1) \rightarrow (4)$ with $\beta_0 = 3.75$ & $\beta_1 = 0.02$ & σ^2 in step(2) equal to 15.3

6- Repeat step $(1) \rightarrow (4)$ with $\beta_0 = 5.79$ & $\beta_1 = 0.999$ & $\sigma^2 = 2.22$.

This yields 10,000 values (or population) of the pairs (X,Y) for each of the models:

$$(1)\quad \mathrm{E(Y_i)} = 1.22 + 0.001X_i$$
$$(2)\quad \mathrm{E(Y_i)} = 3.75 + 0.02X_i$$
$$(3)\quad \mathrm{E(Y_i)} = 5.79 + 0.999X_i$$

$$i = 1,2,...,500$$

4.5 Sampling and confidence intervals:

(I) Take a given population.

(II) Choose a given sample size.

(III) Select a random sample of the given size.

(IV) Estimate β_0 & β_1 by $\hat{\beta}_0$ & $\hat{\beta}_1$

$$\hat{Y} = \hat{\beta}_0 + \hat{\beta}_1 X$$

and from this find the predicted value

$$\hat{X} = \frac{\hat{Y} - \hat{\beta}_0}{\hat{\beta}_1}$$

(V) Calculate the error of forecast $(\hat{X} - X)$ and its square $(\hat{X} - X)^2$

(VI) Calculate a 95% confidence interval for $\hat{X}$ using (2.8)

(VII) If the true value of X falls in the interval put 1 if not put zero.

(VIII) Repeat step (II) to (V) 1000

(VIIII) Count the proportion of time X fall in the calculate interval and also mean of $(\hat{X} - X)$ and $(\hat{X} - X)^2$.

(X) Repeat steps (II) to (VIIII) other sample size in (II)

(XI) Repeat steps (I) to (X) for other population.

4.6Analysis of results:

Table (4.1) summarizes the result of the simulation experiment

Population parameters	Samples size	The percentage of times when the period has contained the true value of $X_{h(new)}$	Mean Mse
$\hat{\beta}_0 = 1.22$	$n = 25$	100%	0.023
$\beta_1 = .001$	$n = 50$	100%	0.0199
$\sigma^2 = 3.4$	$n = 100$	100%	0.2712
$\beta_0 = 3.75$	$n = 25$	99.72%	0.0017
$\beta_1 = .02$	$n = 50$	99.93%	0.779
$\sigma^2 = 15.3$	$n = 100$	99.99%	0.0039
$\beta_0 = 5.79$	$n = 25$	99.31%	0.1817
$\beta_1 = .999$	$n = 50$	99.20%	0.1616
$\sigma^2 = 2.22$	$n = 100$	99.06%	0.1583

Source: The researcher from simulation experiment, MATLAB Package, 2016

From the table we see that in all cases the actual degree of confidence is much large than the stated degree of confidence i.e. 95% However the difference between the two decreases with increase in sample size through slightly.