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Research Article

Cost Analysis of Biliary Drainage Using Metal versus Plastic Stents in Hepatocellular Carcinoma Patients with Obstructive Jaundice

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Keywords
Hepatocellular carcinoma · Obstructive jaundice · Endoscopic retrograde cholangiopancreatography · Metal and plastic stents

Abstract
Background: The optimal method of biliary drainage for biliary obstruction caused by hepatocellular carcinoma (HCC) is controversial, and the possible endoscopic application of plastic and metal stents is the least invasive procedure to improve patients' quality of life. ***Aim:*** Our objective was to study cost evaluation based on a clinical efficacy of both procedures in a randomized trial comparing both approaches in patients with biliary obstruction caused by HCC. ***Methods:*** The strategy of management was based on clinical effectiveness of biliary drainage with either metal or plastic stents in 90 patients over a 1-year follow-up period. Total (direct and indirect) costs were evaluated. ***Results:*** The direct costs were EGP 40,857.84 and 21,802.62 per patient with plastic and metal stents, respectively. Concerning the indirect costs, EGP 888 and 454 were spent for each patient with plastic and metal stents, respectively. The differences in the costs resulted from patients with plastic stent insertion requiring more second endoscopic retrograde cholangiopancreatography procedures and more medication, medical consultation, and hospitalization during the year of follow-up. ***Conclusions:*** Based on this analysis, the use of metal stents rather than plastic stents in biliary drainage is more cost effective for this group of patients.

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Introduction

In 1947, Mallory et al. [1] described the first case of obstructive jaundice caused by the invasion of cystic ducts by hepatocellular carcinoma (HCC) giving rise to biliary obstruction caused by thrombi from the tumor. Thereafter, many varying presentations have been reported. In 1975, Lin et al. [2] classified cases with biliary obstruction caused by HCC as "icteric type hepatoma," this type of HCC manifests with biliary obstruction in the early stage of HCC before the tumor becomes evident clinically or radiologically. HCC can lead to obstructive jaundice by many mechanisms, including growth of the mass until it fills the entire lumen of the ductal system partially or completely, growth of migrated fragments of separated tumor tissue to the lumen of the biliary system, and partial or complete intraluminal blood clots [3].

In such cases, the intra-ductal thrombus is the main reason for biliary obstruction, with an incidence of 1.2–9% [4]. Mixed types of primary liver cancers (cholangiocarcinoma and HCC) have also been found and may represent a further added cause of obstructive jaundice. Infrequently, external compression on the bile ducts is applied by direct tumor encasement or by the enlarged lymphadenopathy at the porta hepatis [5].

Most primary lesions of icteric-type HCC patients are grossly infiltrative or mixed infiltrative and nodular. Usually, no tumor capsule formation can be found in the primary lesion [6]. The infiltrative presentation of this type of tumor may partly explain their early invasion of the portal veins and or biliary system regardless to the type or size of the tumor.

This type of HCC may be present even in the absence of a primary detectable mass [7]. Intraductal tumor is mostly attributed to invasion from the primary lesion and/or from an adjacent extensive malignant portal vein thrombus [8, 9].

Successful endoscopic retrograde cholangiopancreatography (ERCP) procedures date back to the 1960s. Since then, ERCP has come to be the therapeutic modality of choice for pancreaticobiliary diseases [10].

Biliary drainage by ERCP is the standard of care therapeutic modality for biliary drainage in patients with obstructive jaundice and cholangitis. Biliary decompression optimizes the clinical condition that in turn improves the patient's quality of life. Moreover, biliary drainage improves patient survival. Given that simple drainages increase survival between 2.5 and 4.5 months, adding palliative therapies to biliary drainage increases survival from 8 to 13.4 months [11]. Therefore, biliary drainage could improve the prognosis.

In clinical practice, ERCP and stent insertion in patients with HCC does not always seem to be the best therapeutic modality in the context of HCC and biliary obstruction. Some patients with biliary obstruction treated with ERCP and stenting showed incomplete relief of jaundice attributed to the background of liver cirrhosis. Brown and Covey [12] suggested that tumor ingrowth can invade inside the stent, leading to stent dysfunction.

The current modality of drainage is by stenting using metal or plastic stents [13–17]. Metal stents provide a lower stent dysfunction rate and offer prolonged patency over plastic stents. At the same time, patients with HCC and obstructive jaundice have a short survival time [11]. The cost effectiveness analysis between metal and plastic stents has been discussed in many clinical trials. However, the issue has not been studied in the context of HCC based on clinical efficacy and randomization comparing biliary drainage using metal versus plastic stents for obstructive jaundice in regards to cost analysis.

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Patients and Methods

Patients

In the current study, we evaluated 3,064 patients with obstructive jaundice between September 2015 and August 2018. Of these, 1,879 patients were eligible for ERCP, with 100 patients having biliary obstruction caused by HCC, from which 90 patients fulfilled our inclusion criteria. They were randomized for biliary drainage either by plastic or metal stents, thus forming 2 study groups: group I, 45 patients aged 44–73 years old, biliary drainage was achieved by metal stent insertion; group II, 45 patients aged 46–70 years old, biliary drainage was achieved by plastic stent insertion.

Inclusion Criteria

We included all patients with biliary obstruction caused by HCC who were eligible for ERCP according to National Liver Institute protocols. In the setting of obstructive jaundice and HCC, ERCP is the first choice to achieve biliary drainage with the exception of patients with recent band ligation for esophageal varices (within 2 weeks); upper gastrointestinal endoscopy is planned before ERCP if patients have a history of band ligation of between 2 and 4 weeks. All patients ≥18 years with obstructive jaundice caused by HCC during the study period were included.

Exclusion Criteria

All patients unfit for anesthesia, with unsuitable coagulation profiles, previous stenting and dilatation during endoscopy, and HCC with other malignancies were excluded.

Methods

The analysis of costs was based on many studies comparing biliary drainage using metal stents versus plastic stents in the biliary drainage of patients with malignant biliary obstruction. In the current study, we compared the data on the utilized medical resources of all 90 included subjects in addition to the duration of time lost related to the stent occlusion and re-obstruction with its re-evaluation and management. We assessed the direct cost related to the consultation visits, ERCP procedure, imaging, laboratory investigation, hospitalizations, and medications used to treat complications. The indirect cost was calculated based on the time lost (in days) caused by disease burden multiplied by EGP 100 for each day (spent away from daily activity). In the current study, we randomized our patients to receive drainage with metal or plastic stents. The outcomes evaluated included the number of subsequent ERCP procedures and the duration in days away from daily life due to hospitalization. In the current trial, the strategy using metal stents decreased the need for secondary ERCPs and led to reduced complications. The current trial was conducted at the National Liver Institute University Hospital, a well-equipped government-based center for liver disease and endoscopy.

General Considerations for Cost Determination

We included the costs for all of the resources used in both groups of patients, as collected during the period of follow-up. Both the direct and indirect costs were tabulated (Table 1). We conducted this cost analysis assuming that all other factors remained the same outside disease- or procedure-related resources, especially because we only collected disease-related resource utilization, as described above. In other words, we assumed that there were no differences in transportation costs, in personal consumption of pharmaceutical drugs, or in utilization of medical care services other than for the related medical conditions in both groups. All procedures, physician fees, and duration of hospitalization, in addition to the complications related to the disease, were reported in the current trial. Included patients were asked to quantify their time spent away from their usual activity because of re-obstruction and the subsequent procedure or its complications. For each strategy (metal and plastic stenting), the average of total direct costs per patient was computed for each group, including the cost of the ERCP procedures (initial and subsequent), visits and investigations with physician fees (consultation costs were included in all procedures), and all costs of hospitalization.

Follow-Up

The studied patients were randomized to one of the studied groups. They were followed up for 1 year or until re-obstruction or death. Scheduled visits for follow-up were planned monthly. The pertinent periods of hospitalization were recorded, as defined by any hospital admission related to re-obstruction, or any adverse event related to the procedure.

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Table 1. Unit costs

Cost item	Cost value, EGP
Visit (gastroenterology)	150
Consultation (gastroenterology)	300
Total cost for an ERCP procedure with plastic stent application	7,000
Total cost for an ERCP procedure with metal stent application	14,000
Hospitalization for cholangitis	4,224
Average per diem cost for hospitalizations due to biliary re-obstruction	350
Cost of time lost per day	75

Values were rounded to the nearest integer in Egyptian pounds. ERCP, endoscopic retrograde cholangiopancreatography.

Sensitivity Analysis

Analysis of sensitivity was performed regarding the varying medical outcomes through the meaningful range of upper and lower quartiles of the units of the resources utilized multiplied by the costs per unit. Data were recorded and analyzed using SPSS 26 for Windows (SPSS Inc., Chicago, IL, USA). All tests of significance were two-tailed. p values <0.05 were considered statistically significant. Comparison of variables representing continuous not normally distributed data was performed using the Mann-Whitney test.

Results

All cost results were calculated over the 1-year period parallel to the study duration and randomization. The values of cost expressed in this study are presented in Egyptian pounds (given the rapid changes of the value of the Egyptian pound versus the US dollar, we preferred the use of the Egyptian pound).

Direct Costs

Data regarding the used resources are reported in Table 2. Patients with plastic stents required more visits and the average cost attributable to these visits was more than in patients with metal stents. The plastic stent group required subsequent procedures more often and required more hospitalization days, visits, medications, and investigations than patients with metal stenting. Table 3 provides the averages of direct cost for each patient, including the upper and lower bounds based on the utilized medical resources reported in Table 2. ERCP and medications represented around two-thirds of all direct costs in patients with plastic stenting, and three-quarters in patients with metal stenting. For total direct costs, patients with plastic stents cost more money than patients with metal stents.

Fees of Physicians

The physician fees were calculated by direct estimation from the hospital management system.

Costs of Hospitalization

The costs of hospital admission were defined as the daily cost of hospital stay multiplied by number of days spent within the hospital derived from the hospital administration system. This resource included all overhead costs and institutional costs, excluding the fees of physi-

Table 2. Medical resource utilization per patient

	Plastic stent group (n = 45)	Metal stent group (n = 45)	p value
Total visits to gastroenterology	6.56 (1.0)	2.77 (0.4)	0.0001
Total visits to consultants	7.2 (2.1)	3.1 (0.81)	0.0001
Total ERCP procedures	3.6 (1.1)	1.56 (0.32)	0.0001
Total days of hospitalization	5.7 (1.8)	1.65 (0.25)	0.0001
Direct costs, EGP			
Visits to gastroenterology	882.2 (167.3)	334.5 (95.6)	0.0001
Visits to consultants	1,000.1 (241.6)	487.3 (75.9)	0.0001
All ERCP procedures	21,880 (823.4)	14,189 (634.2)	0.0001
Lab investigations	3,378.2 (329.5)	1,320.4 (137.6)	0.0001
Imaging	1,701.4 (401.5)	653.2 (217.5)	0.0001
Medications	5,810.2 (1,080.7)	2,360.3 (732.6)	0.0001
Follow-up	2,178.24 (530.5)	845.12 (198.4)	0.0001
Hospitalization	4,027.5 (1,165.7)	1,612.8 (623.8)	0.0001
Indirect costs, EGP			
Absence from work	1,198.3 (287.3)	600.1 (87.4)	0.0001

Data are presented as the mean (SD). Values were rounded to the nearest 2 decimals. The Student t test was used to assess significant differences in the cost of plastic and metal stents. Differences in both formulas are because each patient differed in number of hospitalizations. Therefore, to calculate the cost of hospitalization per patient we added the number of each patient's hospitalizations then divided it by the total number of patients who were hospitalized, then multiplied by the mean cost of each hospitalization. ERCP, endoscopic retrograde cholangiopancreatography.

Table 3. Total direct and indirect costs

		Patients with plastic stents				Patients with metal stents			
		average cost per patient, EGP	proportion of total direct/ indirect costs, %	lower bound, EGP	upper bound, EGP	average cost per patient, EGP	proportion of total direct/ indirect costs, %	lower bound, EGP	upper bound, EGP
Direct costs	Gastroenterology visits	882.2	2.16	240	880	334.5	1.53	110	330
	Consultant visits	1,000.1	2.45	300	875	487.3	2.24	135	450
	Investigations	3,378.2	8.27	1,000	3,000	1,320.4	6.06	450	1,200
	Imaging	1,701.4	4.16	520	1,550	653.2	2.99	220	600
	ERCP procedure	21,880	53.55	7,500	21,000	14,189	65.08	4,750	14,000
	Medications	5,810.2	14.22	1,900	5,750	2,360.3	10.83	780	2,240
	Hospitalizations	4,027.5	9.86	1,230	3,890	1,612.8	7.39	575	1,580
	Follow-up	2,178.24	5.33	720	2,100	845.12	3.88	284	788
	Total direct costs	40,857.84	100	13,410	39,045	21,802.62	100	7,304	21,188
Indirect costs	Time spent on gastroenterology visits	260	29	120	350	95	21	50	150
	Time spent on ERCP procedures	284	32	130	330	140	31	60	230
	Time spent at hospital	124	14	50	180	61	13	30	100
	Time spent away from ADL	220	25	130	300	158	35	90	250
	Total indirect costs	888	100	430	1,160	454	100	230	730
Total direct and indirect costs, EGP		41,745.84		13,840	40,205	22,256.62		7,534	21,918

Values were rounded to the nearest integer. Low and high values are based on the lower (25%) and upper (75%) quartiles. ADL, activities of daily living; ERCP, endoscopic retrograde cholangiopancreatography.

cians, multiplied by the total average costs per weighted case to express the final costs of hospital admission for each patient. We recorded the per diem costs caused by hospital admissions attributable to complication-related hospital admissions for the studied patients. The per diem costs were the average costs of an adult hospitalization registered for one of the commonly obstructive jaundice-related adverse events and their impacts on costs and hospitalizations.

Table 4. Time lost in days per patient

	Plastic stent group (n = 45)	Metal stent group (n = 45)	p value
Total time spent for visits in gastroenterology	28.78 (8.72)	13.82 (4.6)	0.0001
Total time spent to undergo ERCP	12.29 (4.1)	3.08 (1.0)	0.0001
Total time spent at hospital	42.89 (9.72)	13.23 (4.8)	0.0001
Total of additional time spent away from ADL[1]	16.37 (5.3)	5.42 (1.6)	0.0001

Data are presented as the mean number of days (SD). Values were rounded to the nearest 2 decimals. The Mann-Whitney test was used to assess significant differences in the cost of plastic and metal stents. ADL, activities of daily living; ERCP, endoscopic retrograde cholangiopancreatography.

[1] Differences in the sum of all the days spent away from ADL for all patients/number of patients in both formulas arise because patients had variable numbers of events causing days away from ADL.

Costs of Procedures

We estimated the direct cost for therapeutic ERCP, depending on whether plastic or metal stents were inserted for biliary drainage in the study populations. Additional ERCP procedures were included in the patient's management plan if they developed biliary re-obstruction. In each comparison group, the percentages of procedure repetition as a result of re-obstruction in both groups were 3.6 times in patients with plastic stenting and 1.56 times in patients with metal stenting.

Indirect Costs

Table 4 presents the estimated time lost by each patient relevant to the disease burden (in days). In terms of time lost, all categories of indirect cost (procedures, hospitalizations, and visits, in addition to the time spent away from daily activity), significantly contributed to the total indirect cost burdens. Table 4 shows that patients with plastic stenting required more time away from their daily activity. The total costs are presented in Table 3, demonstrating that the biggest difference came from indirect costs relating to time allocated for procedures followed by time spent away from daily activity in the plastic stenting group, while in patients with metal stenting the time spent away from daily activity was more than the time needed for procedures.

Figure 1 expresses the absolute per patient cost values. On average, the cost for management of a patient with obstructive jaundice in patients with HCC using plastic stents was EGP 41,745.84 versus 22,256.62 when adopting biliary drainage using metal stents (for each patient). In other words, ERCP with biliary drainage using metal stents rather than plastic stents would save on average EGP 19,489.22 per patient.

Indirect Cost Evaluation

Based on a human capital approach [18, 19], the indirect costs were evaluated on the basis of the loss of productivity, based on times lost caused by stent occlusion and or cholangitis. This time is defined as any time lost that resulted in a patient's absence from daily life, and represented the sum of the time, in days, required for procedures, hospital admission, follow-up procedures, and the time needed for medical consultations. The time away from daily activity was reported from patients' questionnaires unless specified as above. The value of a patient's time were evaluated on the basis of the hourly national Egyptian income. For the time consumed away from usual activity, specific hourly values were applied according to the patient's sex and age. For length of hospitalization in addition to the times spent for

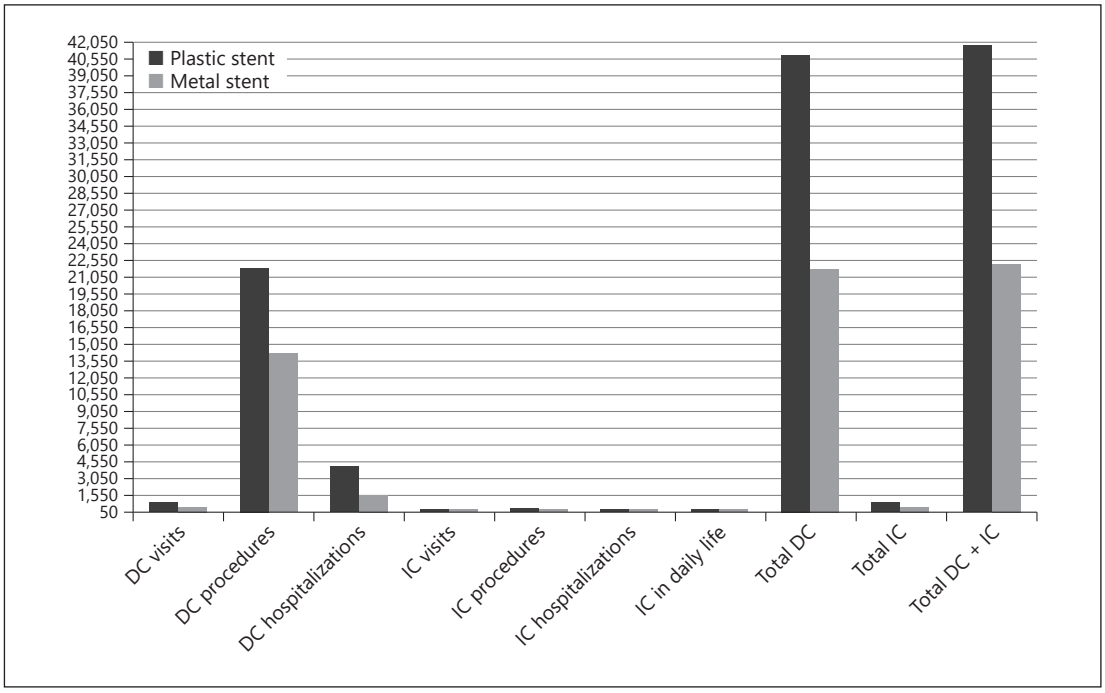

Fig. 1. Per patient costs over 12 months. ERCP, endoscopic retrograde cholangiopancreatography; DC, direct costs; IC, indirect costs.

ERCP, a unified average hourly wage was used for all studied patients. We supposed that each patient spent half a day for consultation visits, imaging, and laboratory investigation, and 1 day to undergo an ERCP procedure. The unit costs are reported in Table 1.

Discussion

Based on the fact that a metal stent has a longer patency time than a plastic stent in patients with pancreatic cancer, periampullary tumors, and cholangiocarcinoma, metal stents are the preferred drainage modality for patients with non-operable and un-resectable malignant biliary obstruction [13]. However, this is not the same for patients with HCC because of the hypervascular nature of the tumor and the underlying mechanisms of biliary obstruction in patients with HCC. Furthermore, HCC has a different tumor biology, coagulopathies, and usually occurs on background cirrhosis where the survival time is shorter [3].

This study compared the cost of ERCP and metal stenting versus ERCP and plastic stenting for the palliation of biliary obstruction caused by inoperable HCCs. With metal stents, tumor in-growth through the metal mesh of the stent remains the major cause of stent occlusion and dysfunction in uncovered stents. In fully covered metal stents, tumor overgrowth and stent migration are the main causes of cholangitis and stent dysfunction. Sludge, bacterial infection, and biofilm formation represent the main causes of occlusion in plastic stents [13]. Therefore, drainages with wider caliber stents have been suggested to function better, and this seems to be the most important factor affecting a stent's life, causing the difference between plastic and metal stents.

Moreover, in HCC stent dysfunctions caused by clogging bacterial colonization are associated with liver failure and worsening of the liver condition and toxemia. Subsequent ERCP

procedures are prevented after failure of drainage or stent dysfunction. However, debate exists regarding which type of stents may be the best draining modality. These uncertainties come from the fact that metal stents offer better patency and fewer subsequent ERCP procedures with their concomitant risks and costs.

In our study, we have quantified the direct cost of all used utilized resources, and also captured the indirect cost caused by time lost by the patients because of their medical conditions and the time lost for diagnosis and treatments. However, we were not able to estimate the fees of transportation and the time-related costs of patients' caregivers. The total costs were EGP 41,745.84 per patient in the plastic stent group and EGP 22,256.62 per patient in the metal stent group, representing a difference of EGP 19,489.24.

ERCP procedures with metal stent application are more expensive than using plastic stents because of the added cost of a metal stent. However, stent dysfunction and/or re-obstruction accrues the expenses of another procedure, further hospitalization, and fees of medical consultations and investigations. Moreover, the patient requires more time away from their daily activities. Thus, there are greater costs resulting from increased numbers of ERCP procedures and higher frequency of hospital admissions among patients with plastic stents. Consequently, direct costs represented the biggest difference between both strategies over a 1-year period.

These findings were not surprising because ERCP with plastic stent application is known to incur more procedures, bearing significantly greater costs. This finding is simply explained by the number of patients who developed stent dysfunction and underwent further ERCP based on their clinical conditions as well as the subsequent hospitalizations noted in patients in the plastic stent group.

In our study, many clinical and methodological issues are worth highlighting. The findings, particularly the information relevant to the clinical efficacy of both strategies and probabilities, are drawn directly from our center. Therefore, our data are not theoretical suggestions and represent the true findings of our clinical observations. Moreover, the clinical relevancies are obviously heightened; indeed, we have reported all used medical resources through the prospective gathering of patients' self-reported questionnaires and actual data in the hospital medical management system. Although our data were more generalizable because the current study was designed to rate cost effectiveness, the findings may still be limited by lack of external validation, especially as we carried out the current study at our center, where the selection of patients was more systematized and organized than in settings in general practice, and also the professionalism of our center in dealing with patients with liver disease as a well-equipped government-based tertiary referral center should be taken into account. However, our trial, to the best our knowledge, is the first such report in the literature to measure the direct clinical impacts of ERCP with plastic and metal stents in the setting of biliary obstruction caused by HCCs.

Another limitation of our study came from the absence of standardization of physician fees in Egypt. However, these fees represented just a small part of the direct costs. We also recorded all required follow-up findings reported by assistant nurses, although 6 diagnoses were identified for the per diem calculation in the current cost analyses (cardiopulmonary, cholangitis, pancreatitis, bleeding, and perforation). Cholangitis and stent dysfunction represented the most commonly encountered complications related to ERCP procedures and remain the major causes of re-endoscopy.

In the medical field, indirect costs are defined as the loss of patient productivity based on the concept of opportunity cost [18, 20]. The cost was computed according to capital approaches in individuals, and is usually applied in the field of medical economics and expressed as an indirect cost and recommended when adopting societal perspectives. Based on the impossible equities in the labor market and other conceptual requirements, even this

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method may lead to overestimates and adopts general assumptions [18, 21–23]. However, the methods of making these estimates remain a matter of controversy [20, 21, 23, 24], with some authors advocating the frictional cost method instead [25, 26]. Unfortunately, this alternative method needs an extensive amount of detailed information, making it seldom applicable [21].

The indirect cost was calculated from the general average wage rate for age and gender for times away from daily activity due to disease burden, either the time spent at the hospital or the post-procedure time spent for follow-up. Hence, it was difficult to estimate the real individual earnings of each studied patient [18, 21, 22]. The calculation of time lost was based on the reported length of hospital admissions, plus the time spent away from daily activities. In addition, we standardized the assumed times of half a day for the investigations and follow-up visits and 1 day for the ERCP procedure. However, the recorded times spent away from daily activity could be affected by the limitation of recall bias. A more accurate approach could be to consider the daily patients' notes regarding time lost away from activities [27] and the necessary transportation times; however, this appears inapplicable in the routine clinical practice.

In this context, we did not calculate the cost of time attributable to caregivers, as it was difficult to estimate in the current study as well as in other studies discussing similar issues. Moreover, the quality of life was not assessed between both groups. Despite the limitations of the current study, to the best of our knowledge it is the first in the literature to address a cost analysis in this context.

Conclusions

The present findings in the current cost analysis were based on a randomized study and compared ERCP strategies with plastic and metal stents, suggested significant differences in the total per patient cost between the groups. The increment of EGP 19,489.24 for each patient favors the metal stent strategy, principally due to the reduced hospitalization and procedural costs; however, larger trials are warranted to study the impact of indirect cost measurements. These data mirror the cost effectiveness findings regarding the cost of ERCP procedures using plastic stents compared with metal stents given the longer patency of metal stents over plastic stents, which decreases the need for subsequent procedures. These findings also emphasize the further advantage of ERCP with metal stents in decreasing the number of cases at a center with a high ERCP volume.

Statement of Ethics

All participants gave their written informed consent relevant to the current study. Ethical approval was obtained in November 2016 from the National Liver Institute ethical committee board (IRB No. IRB00003413) and according to the ethical guidelines of the 1975 Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Conception and design: E.E. Acquisition of data: E.E., W.M. Analysis and interpretation of data: W.M. Drafting the article: W.M., E.E. Revision for intellectual content: E.E., W.M. Final approval of the completed article: E.E.

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