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CLINICAL PROFILE AND MANAGEMENT OF PATIENTS WITH CARCINOMA GALL BLADDER

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Abstract:

Background: Gallbladder cancer (GBC) is an aggressive malignancy and carries an extremely poor prognosis. It is the most common cancer of the biliary tree. The early symptoms of gallbladder carcinoma are generally nonspecific and mimics those of much more common calculous biliary diseases. They present at late stage, and has a dismal outcome with 5- year survival rate is less than 5%.

Patients and Methods: The present study is a prospective observational study that emphasizes the epidemiology and clinical profile of patients who are diagnosed cases of CA Gall Bladder that presented to the Department of Surgery (BPKIHS), Dharan, over a period of One year from September 2017 to September 2018. A total of 30 patients with either diagnosed or Incidental Carcinoma of Gall Bladder were included in the study.

Results: Most presented within 6 months (n=26, 86.6%) of becoming symptomatic. The median duration of illness was 2±5.89 months ranging between 0.5 to 24 month. Transabdominal ultrasonography detected the disease in 26 (86.6%) of the 30 surveyed cases, most common site involved being the fundus and body (76.9%). Out of 14 cases who proceeded for surgery based on CT resect ability, intra-operatively seven (50%) were unresectable, three due to metastasis and, four due to locally advanced disease with hilar infiltration. Total seven patients underwent radical resection with curative intent.

Conclusion: In the present study of gallbladder carcinoma, it is evident that most tumours present in a middle age group with female predominance, and are predominantly unresectable at the time of presentation, signifying towards a poor prognosis disease

Keywords
Ca Gall Bladder, Inoperable Cholecystectomy, Unresectability

Introduction

Gallbladder cancer (GBC) is an aggressive malignancy and carries an extremely poor prognosis. It is the most common cancer of the biliary tree.[1] These patients usually have no specific presenting symptoms, and therefore present with a late stage disease, which corresponds to poor prognosis. The extensive variation in geography, ethnicity, and cultural differences in the incidence of gallbladder cancer suggests the role of key genetic and environmental factors associated with the development and progression of the disease.[2,3] Incidence varies according to geographical region, with residents of Indo-Gangetic belt particularly females of northern India (21.5/100000) and south Karachi Pakistan (13.8/100000) being reported as one of the highest affected regions.[4] Elsewhere, the annual incidence is of 1 or 2 people per 100,000 population. [5] The early symptoms of gallbladder carcinoma are generally nonspecific and mimics those of much more common calculous biliary diseases. They present at late stage, and has a dismal outcome with 5- year survival rate is less than 5%.[6] Hepatic invasion and metastatic progression is one of the major cause of its poor prognosis. Carcinoma gallbladder is an orphan disease with minimal research efforts currently (both basic and translational), due to its rarity. This is also the scenario in Nepal where very few studies exist documenting the disease. Therefore, there exists opportunity to study the profile and presentation of a case of GBC in our setting. We took up a prospective study of all the gallbladder cancer patients presenting to our tertiary care hospital in Eastern Nepal over 12 months period to study (which has not been done before) the profile, pathological status, resectability and short term outcome.

Patients and Methods:

The present study is a prospective observational study that emphasizes the epidemiology and clinical profile of patients who are diagnosed cases of CA Gall Bladder that presented to the Department of Surgery B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, over a period of One year from September 2017 to September 2018. A total of 30 patients with either diagnosed or Incidental Carcinoma of Gall Bladder were included in the study.

Ethical clearance was taken from the Institutional ethical review board before the start of the study. Diagnosis of carcinoma gallbladder was made on basis of clinical history, ultrasonography and Contrast enhanced computer tomography (CECT) abdomen. If Contrast Enhanced Computer Tomography abdomen showed the tumour to be resectable, then patient was taken up for surgery for radical resection. The study also

included incidental gallbladder cancer with its incidence and stage.

The defined criteria for unresectability:

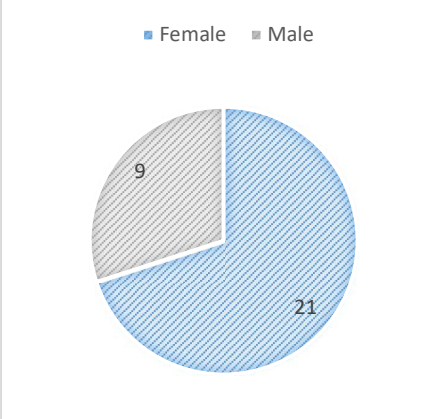
1. Distant metastasis
2. Lymph node involvement outside the hepatoduodenal ligament.
3. Involvement of secondary confluence (confluence of segmental ducts to form right or left bile ducts) of both lobes of liver
4. Involvement of main portal vein or proper hepatic artery.

If there was no metastasis on exploration, then the patient underwent extended cholecystectomy, which includes partial hepatectomy with resection of gallbladder fossa. Histopathologic examination was done to evaluate the type of tumour, resection margin (R0), number of lymph nodes harvested, lymph node metastasis and ratio. Post-operative outcome were assessed as postoperative length of hospital stay, overall morbidity (on the basis of Clavien-Dindo classification of surgical Complications), and any 30-and 90-day mortality. Follow-up: The records of Post-operative adjuvant chemotherapy, the patient received and completed were entered. Patients were followed up for a minimum of three months post operatively for any recurrence.

RESULTS

Over a period of one year (1st September 2017 to 1st September 2018), 30 patients were diagnosed with carcinoma gallbladder and were included in the study.

Out of 30 cases, 21 (70 %) were females and 9 (30 %) were males. The female to male ratio was 2.33:1(Fig. 1). The age of the patients in the study ranged between 35 to 85 years. The mean age of the patients was 55.83±14.2 years, most of the patients fell into the age group of 35-45 years (n=9) (Fig.2).



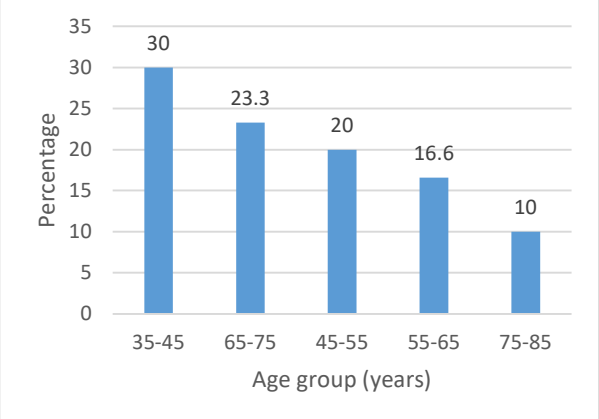


Figure 1: Gender distribution of study group

Figure 2: Age distribution of study group

Majority of cases in this study were from east Nepal with 23.3 % (n=7) of patients from Sunsari, and 20% (n=6) from Jhapa District, 13.3% (n=4) from Saptari, and Dhankuta respectively. In our study, most patients presented within 6 months (n=26, 86.6%), two (6.6%) became symptomatic between 6 months to 1 year and 2 came with symptoms beyond 1 year. The median duration of illness was 2±5.89 months ranging between 0.5 to 24 month. At the time of admission, majority of the patients (n=19, 63.3%) had an ASA Grade of II, 11 Patients (36.6%) admitted had an ASA Grade III. Most common presenting symptom was right upper quadrant pain (n=28, 93.3%), anorexia was also common, seen in 22 (73.3%) patients, weight loss in 21 (70%) patients, obstructive jaundice in 17 (56.6%) whereas vomiting due to gastric outlet obstruction in 2 (6.66%) . Three Patients (10%) had acute calculus cholecystitis in the past, three had associated acute cholangitis in the past. During a pre-operative clinical examination, 8 (26.6%) patients had a palpable gallbladder and 3 (10%) patients Physical Examination had ascites on per abdominal examination. Three of the patients (10%) had clinical evidence of metastasis as they had ascites at presentation. Assessment of pre-operative liver function test showed an abnormal total bilirubin, which ranged from 0.2 to 35.9 mg/dl with the median value of 7.7 mg/dl, in 20 (69%) cases and direct bilirubin, which ranged from 0.1 to 28.5 mg/dl with a median value of 5.2mg/dl ,in 20 (69%) cases. Elevated alanine aminotransferase (ALT) was seen in 21 (72.4%) cases with a median value 58 U/L and ranged from 10 to 325 U/L. Aspartate aminotransferase (AST), with a median value of 77 U/L, was elevated in 24 (82.8%) cases, while ALP, with median value of 258 U/L ranging from 74 to 1491 U/L. , was increased in 23 (79.3%) cases. Total protein was decreased in 11 (37.9%) and serum albumin was decreased in 15 (51.7%) cases. The median total protein was 6.8 gm/dl which ranged from 4.7 to 9 gm/dl and median albumin level was 3.4 gm/dl which ranged from 2.1 to 5.5 gm/dl. Anaemia (<10mg/dl) was seen in 12 (41.4%) cases with a median value of 10.25 ranging from 7.8 to 13.6 g/dl (Table 1).

Table I: Laboratory investigations

Parameters	Normal		Deranged		Derangement		Median (Min-Max)
	No.	%	No.	%			
Hemoglobin	18	60	12	40			10.25 (7.8-13.6)
Total Bilirubin	10	33.3	20	66.6	1.4-4.2	4	7.70(0.2-35.9) mg/dl
					>4.2	16	
Direct Bilirubin	10	33.3	20	66.6	0.2-0.6	2	5.2 (0.1-28.5) mg/dl
					>0.6	18	
ALT	9	30	21	70	41-82	10	58 (10-325) U/L
					82-123	6	
					>123	5	
AST	6	20	24	80	38-76	9	77 (17-184) U/L
					76-114	6	
					>114	9	
ALP	7	23.3	23	76.6	130-260	9	258 (74-1491) U/L
					260-390	6	
					>390	8	
Protein	19	63.3	11	36.6			6.8 (4.7-9) gm/dl
Albumin	15	50	15	50			3.4 (2.1-5.5) gm/dl

Transabdominal ultrasonography detected the disease in 26 (86.6%) of the 30 surveyed cases, most common site involved was the fundus and body (76.9%) in any 20 cases, followed by neck (26.9%) in 7 cases . Intrahepatic biliary radicle dilatation was seen in 17 cases (65.3%) with all being in both lobes of the liver, The most common level of obstruction was at the confluence, a majority of the cases (n=17, 65.3%) surveyed had associated gallstones. Also, chest x-ray for all cases showed no signs of distant metastasis.

Total 30 cases underwent CECT abdomen, out of them, resectability was seen only in 16 (53.4%) cases, with 14 (46.6%) cases were unresectable due to metastases or major vessel involvement in the hilum.

Out of 17 cases of clinical Jaundice, PTBD was attempted in 5 cases (17.24%) as a palliative measure for the relief of obstructive jaundice. It was technically and clinically successfully in 3 (10.34%) cases. However, in two (11.7%) cases, it was technically unsuccessfully.

Out of 14 cases who proceeded for surgery based on CT resectability , intra-operatively seven (50%) were unresectable, three due to metastasis and, four due to locally advanced disease with hilar infiltration. Total seven patients underwent radical resection with curative intent. The two unresectable patients underwent palliative intervention for Gastric outlet obstruction (GOO) and obstructive jaundice.

Incidental Carcinoma gallbladder

Four (13.3%) patients had incidental gallbladder carcinoma in our study, one (3%) was staged as stage II and three (9%) as stage IB. Among them two underwent extended cholecystectomy with curative intent. Two (6%) patients post operatively refused for completion extended cholecystectomy, one due to poor performance status in view of age and comorbidities and other one due to financial constraints. Both were lost to follow up.

Histopathology

All 14 operated cases (curative and metastases) had samples taken for histopathological examination, all of the tumours assessed were adenocarcinomas. The mean lymph node harvested and the lymph node ratio were 4.2±2.5 (range: 2-8) and 0.5±0.1 (range: 0-0.5) respectively. Regarding histopathological AJCC TNM Staging of the seven curatively resected, 4 (57.1%) had T2NxM0R0, 2 (28.5%) had T3NxM0R0, whereas one (14.28%) had T3N1M0R0 (Fig 3).

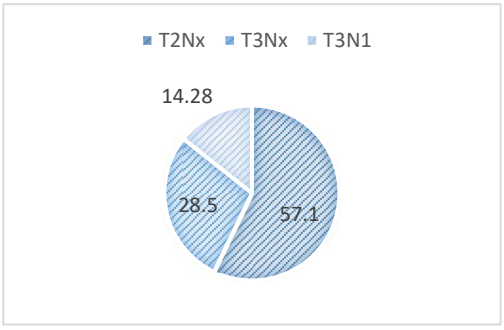


Fig 3: Post-operative Staging

Out of 30 cases, it was seen that 21 (70%) had a staging of IV B, alluding to incurability and non-resectability. Five cases (16.6%) had a staging of II, and one (3.4%) had a staging of I B, III A, III B and IV A respectively (Table 2).

Table II: Histopathology: TNM staging (%)

AJCC STAGE	Curative resection	Intra-operative unresectable/palliative	Non-Operated	Total (n=30)
I B	1			1
II	3		2	5
III A	1			1
III B	1			1
IV B		7	14	21
IV A	1			1

Post-operative Outcome

The mean post-operative length of hospital stay was 6.1±5 days ranging from 2-15 days. The postoperative morbidity was seen in 20% of patients. As per Clavien-Dindo classification, the minor and major complications were seen in 5 (16.6%) and 1 (7.14%) patients respectively. The details are as described in the Table 9.

One patient had a major complications following extended right hepatectomy with bile duct excision, in the form of localized bilioma requiring pigtail drainage. Rest of the minor complications were managed conservatively.

There was no surgery related mortality (in hospital and 90 -days) in the curative intent group. However, there was one (7%) 30- day mortality in palliative intent group.

Following curative intent, 4 patients (57%) received adjuvant chemotherapy and completed the cycles. Remaining 3 (43%) patients failed to receive adjuvant therapy. In the metastatic group, only 4 (17%) received adjuvant therapy.

In curative intent group, all patients are alive till the conclusion of the study, with recurrence in one case at 12- months of surgery. In unresectable group as of last follow up, 16 patients had died of disease at 6 months follow-up (Table III) after excluding (four patients who lost to follow up).

Table III: Follow up at 6 months

Follow up (total n=30)	Died Of disease	Follow up loss	Alive- with disease	Alive- without Disease
Curative Intent(n=7)	0	0	1	6
Palliative Intent (n=7)	4	1	2	0
Metastatic/non-operated (n=16)	12	3	0	0

DISCUSSION

This study confirms that patients having gallbladder carcinoma have very poor prognosis. Possible management strategies should be evaluated in the light of the natural history of the disease, survival benefit, morbidity and mortality rates, and patient co-morbidity. Many studies have reported that T-stage or stage-grouping are of positive predictive value, although the small numbers of patients with early disease has not allowed a significant correlation with survival. This also helps refine indications in patients found incidentally and treated surgically for locally advanced gallbladder carcinoma. Only patients with complete resection (R0) showed a survival benefit from resection. Nepal has the fifth highest incidence of carcinoma gallbladder in the world[7], with a preponderance for females.[2] In our study, gallbladder cancer was high in females (70%) with a female: male ratio 2.33:1. This is in correlation with the global trend where it is commoner in females, with male to female ratio ranging from 1.3:1, in the study conducted by Miller G et al [8], to as high as 3.81:1 in the study from India. [2] The mean age in our study was 55.83±14.2 which is similar to other studies by Miller G et al [8] (mean age: 40) and Khan et al [2] (mean age 65) respectively. Out of all cases, 13.3% were incidental carcinoma gallbladder carcinoma. This is high compared to the findings of similar study from Nepal, where the incidence was only 1.28% [9]. However, in the west, the incidental gallbladder cancer covers around 70% [10] of total gallbladder cancer. The good thing about incidental is that with curative intent resection, the 5-year survival is higher than non-incidental (70% vs 20%).[11,12] Hence, this higher incidence of incidental carcinoma gallbladder questions the role of prophylactic cholecystectomy in the patients with asymptomatic gallstone disease in the backdrop of high incidence as poor accessibility.

Obstructive jaundice in a patient with gallbladder carcinoma is a sign of advanced disease with a grim prognosis because of associated locally advanced and/or metastatic disease. It is also associated with high perioperative morbidity and mortality with curative resection. Around 7% of patients are resectable, as quoted by Agrawal et al.[13] In our series, out of 30 patients, obstructive jaundice was observed in 57% of patients which is higher (two times) than the global trends, where incidence ranges from 25 to 35%.[14,15] Out of 17 jaundiced patients, only one patient (5.8%) with obstructive jaundice underwent extended resection (Extended right hepatectomy) with curative intent. Rest of the patients were already having advanced disease due to the metastases (17%) and hilar infiltration (76%). However, palliative biliary drainage for relief

of jaundice was done 10% of patients, with two (11%) undergoing T-tube drainage and one (3%) undergoing hepatojejunostomy. The results were similar to the experience by Hawkins et al, who had 34% of their patients presenting with obstructive jaundice. Only six (7%) jaundiced patients were resected with curative intent, with only four (5%) having negative surgical margins.[14] Two of them died perioperative and the remaining 4 experienced disease recurrence within 6 months after surgery.[14] In the present study, our patient had a recurrence at 15 months following surgery. In a study conducted in New Delhi by Agarwal and colleagues, the resectability rate of patients with obstructive jaundice, operated by curative intent was 27.45%, with mortality being 7.14% and morbidity being 50%. The mean disease free survival was 23.46 months.[13] Our findings are also concordant with those of Dasari B et al[16] who in a systemic review concluded that not only do patients with jaundice are less likely to have resectable disease, but also that radical surgery in patients presenting with obstructive jaundice is associated with reduced overall survival and increased postoperative morbidity. However, the subsequent studies from the other institutions of the world have shown a modestly improved survival outcomes after surgical resection in the setting of jaundice, including studies from Japan (median survival of 18 months), China (14 months), India (26 months) and France (11 months).

Ultrasound and Computed tomography is the initial investigation modality of choice for diagnosis and staging of the disease. In our study, it was observed that out of 16 CT scan based resectable tumours, only 7 (43.75%) patients were resectable at surgery. In 56% of cases, it underscored the staging. The under-staging was due to the omental and peritoneal metastases, and major vessel involvement at the hilum. On staging by AJCC 7th edition 46.6% fell under stage IV B, 20%, under stage II, 10% fell under stage III A, III B, and I B respectively, and 3.3% under IV A. This appears to be similar to the result seen by George R et al wherein Stage IV B was seen in 44% cases followed by stage II (18%) and IV A (16%)(17). This under-staging by contrast CT can probably be overcome by use of newer diagnostic modalities for staging like 18 fluorodeoxyglucose (FDG)-PET/CT scan, which is valuable for detecting regional lymph node involvement and unsuspected distant metastases that are not diagnosed by CT. [18]

The mainstay of treatment for gallbladder cancer is radical en-bloc cholecystectomy (extended cholecystectomy, extended hepatectomy or combined resection of adjacent organs). The type of treatment depends on the stage of the diseases. Unfortunately, only 10 to 30% of patients are resectable at surgery with curative intent. In the present study, only 7 (23.3%) patients were resected with a curative intent, while the remaining 5 (16.6%) required

some form of palliative procedure for gastric outlet obstruction and jaundice. This is in favour with the experience by Kumaran V et al who, found only 5 (16.1%) patients to undergo curative resection out of 31 gallbladder cancer(19). Similarly in a retrospective study by Mohammed Yousif et al from Saudi Arabia, out of 76 patients with gallbladder cancer, only 31 (40.8%) patients were resectable based on clinical and CT staging and evaluation. On further surgical resection attempt, radical cholecystectomy with curative intent was accomplished in only 21 (27.6%) patients.[20] This gives the overview of the Gallbladder cancer resectability, with only a quarter of patients diagnosed are resectable with a curative intent. Moreover the extended resection are required in up to one-third of the patients, as seen in our study (1 out of 7, 14.2%).[21]

All the tumours assessed were adenocarcinomas (NOS) which is the primary type of tumour as supported by various studies.[22,23] The mean lymph node harvested were 4.2±2.5 with the ratio being 0.5±0.1. Lymph node ratio is a strong predictor of disease free status. Such are also the findings of Negi et al[24] who advocated at least 6 intra-operative node biopsies to assess staging. Tsukada K and colleagues[25] were of the opinion that lymph node metastasis of N1 are curable by radical resection in >50% cases. It has been reported that the frequency of lymph node involvement in gallbladder cancer is strongly influenced by the depth of carcinoma invasion in the primary tumour.[26-29] Ogura et al, have reported based on the analysis of 1686 resected cases with GBC collected from 172 hospitals in Japan, that 2 types of primary tumour (those with serosal involvement and those invading adjacent organs) have a high frequency of lymph node involvement: 72% in the serosal group and 74.4% in the adjacent organ group. Tumours confined to the gallbladder had a relatively low frequency of lymph node involvement (44.3%).[26] In our study the low lymph node ratio (0.5±0.1) in resected cases favours this outcome. Gallbladder cancer extending beyond the serosa or invading adjacent organs spreads exclusively and widely into the lymph nodes around the head of the pancreas. This suggests that an accurate estimation of the depth of tumour invasion, assessed prior to surgery or intraoperatively, may be helpful for choosing the appropriate surgical procedure for lymph node dissection.

Radical resection of GBC is a major abdominal surgery with an overall morbidity rate of 14 to 53% and a 90-day mortality rate up to 8% due to the extended resection.[21] Most of the complications are minor and are pulmonary, cardiac, sepsis and bile leak. In the present study, most of the complications were minor, with only one major complications due to the bilioma requiring percutaneous drainage. There

were no 90-day mortality in the curative intent resection group.

Similarly, the overall survival of patients with Gallbladder cancer depends on the stage of the disease. The 5 year survival is approximately 50% in stage I, 28% in stage II, 8% in stage III A, 7% in III B, 4% in IV A and 2% in IV B .[29] It also depends on the resection margin positivity, completion of adjuvant chemotherapy and more importantly an aggressive tumour biology in our settings. Even after surgical resection, the overall survival for patients with GBC is poor suggesting the role for adjuvant systemic chemotherapy. Takada et al. performed a phase III prospective randomized control trial in 112 patients with gallbladder carcinoma with 69 patients treated with mitomycin C and 5fluororouracil and 43 patients treated with surgery alone; the 5-year overall survival and 5-year disease-free survival were higher in the treated groups compared to the control group. Recently, Edeline et al, reported in the PRODIGE 12-ACCORD 18 phase III trial that patients with biliary tract cancer treated with gemcitabine and oxaliplatin did not have a statistical difference in median relapse-free survival compared to placebo.[30] In our patients, although the mean life expectancy of the palliative treated group came out to be 3.78±2.3 months and that of the non-operated came to be 1.41±1.2 months. All curatively resected cases were alive at the conclusion of the study. Four of these received full cycles of Gemcitabine based adjuvant chemotherapy. Whereas majority (n=16, 53.3%) of the unresectable and palliated patients had expired due to the disease at 6 months of follow-up. We had one incidence of recurrence at 15 months of follow up, which is in line with the findings published in 2016 by the US extrahepatic biliary malignancy consortium that published data on 217 patients who underwent curative intent surgical resection at ten academic institutions. Here, the median time to recurrence was 9.7 months.[31] Given these significant recurrence rates, post-operative surveillance strategies are essential for detecting tumour recurrence, but must be coupled with more effective treatment regimen. Currently the survival rate for patient with resected gallbladder carcinoma remains dismal. (1 , 3, and 5 year survival rate being 56,30 and 21 respectively).[32]

Conclusion:

In the present study of gallbladder carcinoma, it is evident that most tumours present in a middle age group with female predominance, and are predominantly unresectable at the time of presentation, signifying towards a poor prognosis disease. Tumours generally present late, with more than 50% patients presenting with obstructive jaundice (an ominous sign of unresectability). However, small percentage (one-quarter) of patients, including incidental GBC are resectable with curative intent (with an acceptable postoperative overall morbidity

and mortality) with a favourable prognosis and an acceptable postoperative.

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1.Yadav R, 2.Rajesh TK, 3.Mittal V
Work concept and design 1,2,3
Data collection and analysis 1,
Responsibility for statistical analysis 1
Writing the article 1,2,3
Critical review, 1, 2,3
Final approval of the article 1,2,3

Each author believes that the manuscript represents honest work and certifies that the article is original, is not under consideration by any other journal, and has not been previously published.
Availability of Data and Material: The corresponding author is prompt to supply datasets generated during and/or analyzed during the current study on wise request.

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