Cohort Study

Biliary complications after adult to adult right-lobe living donor liver transplantation (A-ARLLDLT): Analysis of 245 cases during 16 years period at a single high centre- A retrospective cohort study

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ABSTRACT

Objectives: Biliary complications (BCs) after adult to adult living donor liver transplantation (A-ALDLT) result in poor graft and patient survival. This study aimed to analyze these complications.

Methods: We retrospectively analyzed BCs in 245 recipients who underwent A-ALDLT using the right-lobe graft during 16 years period in our centre. The overall male/female ratio was 215/30.

Results: One hundred fifty-five BCs affected 102 of our recipients (95 early (≤3 months) and 60 late (≥3 months)). They were classified as 67/245 (27.3%) early bile leak, 10/245 (4.1%) early biliary stricture, 44/245 (17.9%) late biliary stricture, 4/245 (1.6%) early cholangitis, 10/245 (4.1%) late cholangitis, 14/245 (5.7%) early biloma, and 6/245 (2.4%) late cholangitic abscesses. Multiple biliary anastomoses were independently correlated with Post liver transplantation (LT) overall BCs; moreover, post LT hepatic artery thrombosis or stenosis (HAT/S) was an independent predictor of overall BCs, strictures and leaks. The mortality affected 96 (39.2%) cases mostly due to sepsis, bleeding and multi-organ failure (MOF). On the other hand, the biliary related mortality was 10.6% of cases. Multiple cholangitic hepatic abscesses were significant predictors of poor graft and patient outcomes.

Conclusions: Multiple biliary anastomoses and post LT HAT/S lead to a poor biliary outcome, furthermore, cholangitis, cholangitic abscesses and sepsis lead to poor graft and patient outcomes, so proper management of those variables is mandatory to improve outcomes after A-ARLLDLT.

1. Introduction

Despite improved surgical techniques, perioperative care, organ preservation and immunosuppression in living donor liver transplantation(LDLT); biliary complications (BCs) (i.e. bile leaks, biliary strictures, cholangitis, biloma, cholangitic abscesses, bile duct stones/casts, ischemic biliary injury, hemobilia, sphincter of Oddi dysfunction (SOD), etc) remain a significant catastrophe after adult to adult right lobe LDLT (A-ARLLDLT) leading to post-transplant morbidities, dysfunctions and mortalities. [1,2]; they may reach up to 60% of recipients [3–11].

They are related to various sources (i.e. Graft bile ducts (sizes, numbers and anatomic variations), biliary ischemic damage (hepatic artery complications, warm and cold ischemia times, ischemiareperfusion injury (IRI), etc), biliary reconstruction related factors (reconstruction type and number, suture methods and materials and t-tube/stent use/non-use), immunologic issues (ABO incompatibility) and infections (biliary sepsis and cytomegalovirus (CMV) infections) [1,12,13].

They can be identified clinically (abdominal pain, distension, bilious drains or wound, jaundice, fever, sepsis, etc), biochemically (abnormal liver function tests(LFT), etc) and by imaging(abdominal ultrasonography(US) including Doppler US, abdominal computed tomography(CT) including CT angiography, magnetic resonance(MR) imaging (magnetic resonance cholangiopancreatography(MRCP) and MR angiography), external stent/t-tube cholangiography, percutaneous transhepatic cholangiography(PTC) and endoscopic retrograde cholangiopancreatography(ERCP) [1,12].

There are different treatment options for those complications (i.e.
conservative treatment (i.e. wait and see), endoscopic management (i.e. ERCP), percutaneous interventions (i.e. percutaneous drainage (pigtail) and percutaneous transhepatic biliary drainage (PTBD) and lastly surgeries (i.e. surgical drainage, external biliary diversion and hepaticojejunostomy (HJ)) [2,12]. However, the non-surgical management of these catastrophic complications became the commonest therapeutic option after advances in endoscopy and interventional radiology measures [2].

In the literature of a large number of cases; the analysis of BCs after A-ARLLDLT is scarce, so our aims and objectives were to analyze those complications and their predictors as well as patients outcomes during 16 years period at a single high tertiary Egyptian centre.

2. Materials and methods

After approval of our institutional review board (IRB), we did this cohort study which is a retrospective analysis of a prospectively collected database done in a single institution. It analyzed BCs after A-ARLLDLT in the department of hepatopancreato-biliary (HPB) surgery, National liver Institute (NLI), University of Menoufiya, Menoufiya, Egypt; in the period from December 2003 to December 2019 where patients were observed from POD1 until the end of December 2019 or until the death of patients with a median follow up period of 34(range; 0.03–192) months.

Our study included 245 patients after exclusion of cases that refused research, cases with loss of data and those who did not complete the follow-up. The data were collected from our liver transplant (LT) unit. The recipients and their donors gave written informed consent regarding surgeries and research, furthermore, our work was registered in the research registry with registration NO of researchregistry4596(www. researchregistry.com) as well as it was reported in line with the STROCSS 2021 criteria [14]. All our donors were ≥19 years old and were pre-operatively assessed clinically, psychologically, biochemically ((LFT), virology, etc), pathologically (liver biopsy), and by imaging (abdominal US, CT volumetry, CT angiography, and MRCP; Fig. (1: A, B)) [15–17].

The collected variables included: A- Preoperative variables: Donors parameters (i.e. age, gender, donor liver biopsy, etc) and recipients’ parameters (i.e. age, weight, gender, Child-Pugh(CTP) and Model for end-stage liver disease (MELD) scores, original liver disease, co-morbidities, pre- LT portal hypertension(PHN) and portal vein thrombosis(PVT), etc) [15–17]. B- Intra-operative variables: Graft type, No of hepatic artery (HA) anastomoses and their difficulties, No of biliary anastomoses; their types and suture types, as well as liver graft bile ducts (BD) No, ductoplasty, using biliary stents, actual graft weight, and graft recipient weight ratio (GRWR), cold, warm ischemia and HA anastomosis times per minute, blood and plasma transfusion per units and operative time per hours [15–17].

...Donor procedure: It was done by a qualified team; in brief; After mobilization of the right lobe (RL) of the liver and dissection of IVC, an intra-operative cholangiogram was performed routinely through the cystic duct after cholecystectomy and before parenchymal transection to delineate the biliary anatomy and the correct point of biliary transaction (Fig. 1C). The right portal vein (RPV) and right HA (RHA) were isolated with excessive peri-ductal dissection to minimize ischaemic damage to the BD. The cavitron ultrasonographic surgical aspirator (CUSA) + bipolar devices were used to divide the liver parenchyma without inflow occlusion. After parenchymal transection, minimal dissection of hilar peribiliary soft tissue was done without cauterization. Then, the right BD/s was/were divided with sharp scissors maintaining more than 2–3 mm safe margin from biliary bifurcation to prevent stricture of the remnant donor liver duct. Then, we closed the opening of the remnant liver BD using continuous 6-0 prolene sutures. A final cholangiogram was then performed at the end of the operation to ensure biliary tract...
integrity. Then, on the back table; the harvested graft was flushed and preserved in Hydroxytryptophan ketoglutarate (HTK) solution and weighted to determine the actual graft weight and GRWR. Moreover, in grafts with multiple BDs; ductoplasty of the adjacent ducts was done to obtain a single orifice using a continuous 7-0 prolene suture [15–18].

Recipient procedure: It was done by a qualified team; In short; the recipient BD was prepared by doing a minimal dissection of the pericholedochal soft tissue aiming to leave as much of the vascular connections between the BD and the HA intact as possible and to preserve the 3 and 9 o’clock arteries; moreover, sharp scissors were used for BD transection above the hilar bifurcation. The biliary anastomosis was performed using loupe magnifications after completing vascular anastomoses. Tension-free duct to duct (D-D) or R-Y HJ reconstruction was selected according to graft and recipient BDs site and size matching. The recipient common hepatic duct (CHD) was mostly used for a single anastomosis, however, the right hepatic ducts (RHDs) and left HD (LHDs) were mostly used for double anastomoses. The posterior and anterior layers of biliary anastomoses were performed using interrupted 6-0 Polydioxanone(PDS)/prolene sutures keeping a 1mm distance between stitches, furthermore, an external 4–6 Fr polyethylene tube (external stent) was used selectively by the surgeon’s decision for biliary decompression and to drain bile for 1month after LT before being clamped and then removed at the 6th–8th months from LT after ensuring absent BCs by repeated cholangiography [15–18].

C- Postoperative management: 1- Prophylactic antibiotics: By giving preoperative 3rd generation cephalosporine, then intra/postoperative tazobactam plus metronidazole or imipenem plus metronidazole until culture results. 2- Prophylactic anticoagulants: Starting with heparin infusion until POD8; the time of giving dipyridamole. 3- Immunosuppression regimens consisted of a triple-drug therapy that included calcineurin inhibitors (CNIs)(tacrolimus or cyclosporine), mycophenolate mofetil (MMF), and steroids. When CNIs were contraindicated or had side effects; sirolimus (SRL) or everolimus were given. Steroids and MMF were completely withdrawn at the end of the 3rd and 6th postoperative months respectively. In late cases; an interleukin-2 receptor blocker (Simulect) was administered on POD0 and 4 for reducing the CNI dose [15–17].

D- Postoperative follow-up (by a team consisting of transplant surgeons, hepatogastroenterologists, and radiologists) was done daily until hospital discharge, then monthly during the 1st 6 months, then every 3 months until the end of 1st year, then every 6 months until the end of the follow-up period for detecting: A-HA thrombosis or stenosis (HAT/S) that were diagnosed when the LFTs became abnormal or when doppler US showed poor or no blood flow within HA and were confirmed by doing CT angiography, MR angiography or formal conventional angiography if needed. B- BCs that were known by clinical assessment (i.e. bilious drains, etc), abnormal LFTs and/or the abdominal US and were confirmed by external stent cholangiography, MRCP; Fig. 2, and when necessary ERCP (for D-D cases), PTC (for HJ cases) or abdominal CT (for bile leak, biloma and cholangitic abscesses cases); they were classified into early and late complications if occurred (<3months) and (≥3months) from LT respectively [15–17].

E- HAT/S was managed by anticoagulant therapy, angiographic (dilatation, thrombectomy, thrombolytic therapy and/or stenting) or surgical thrombectomy and/or reconstruction. On the other hand; BCs were managed by conservative therapy, percutaneous drainage (single or multiple pigtail insertions), ERCP shinectrotomy ± dilatation ± Stenting; Fig. 3, PTBD; Fig. 4, open surgical drainage, external biliary diversion and/or by R-Y HJ; Fig. 5. Graft and patient survivals, as well as mortality causes, were recorded during the follow-up period [15–17].

SPSS 21 software was used for the statistical measures. Qualitative data were expressed in frequency and percentage and analyzed with the Chi-square or Fisher exact tests. Quantitative data were expressed as the mean and standard deviation or median (range) and were compared with the t- or Mann- Whitney U tests. Univariate and then multivariate analyses were performed for determining predictors of BCs as well as predictors of graft and patient survival. The Kaplan–Meier method was applied for survival analysis and comparisons were done using log-rank tests. In all tests, a P-value of <0.05 was significant [15–17].

3. Results

3.1. The patients’ characteristics

They were classified as 215(87.8%) males and 30(12.2%) females. Their median age and body weight reached 47 (range; 22–66) years and 80 (range; 43–120) kg respectively. Their donors were categorized into 176(71.8%) males and 69(28.2%) females, where, median age and BMI were 26 (range; 18–45) years and 26 (range; 18–35) respectively. The 1st-degree donor to recipient relation was the most frequent 121
The normal, peri-portal fibrotic (PPF), and steatotic donor liver biopsies were 85.7%, 9.8%, and 4.5% respectively. The recipients’ median MELD score was 16 (range; 7–34), moreover, CTP scores A, B, and C were 13(5.3%), 64(26.1%), and 168(68.6%) respectively. The co-morbidities (DM, hypertension, cardiac disease, etc) affected 26.1% of them while Pre LT PVT and PHN affected 15.5% and 91.4% of them respectively. Table 1.

The compatible and identical donor to recipient blood group matching were 73(29.8%) and 172(70.2%) respectively. The RL-middle hepatic vein (MHV), RL+MHV and Segments VI, VII liver grafts were given to 234(95.5%), 10(4.1%) and 1(0.4%) of them respectively. The single and double HA anastomoses were performed in 229(93.5%) and 16(6.5%) of them respectively, however, the anastomosis was difficult in 5(2%) of patients. The single and multiple liver graft BDs involved

121(49.4%) and 124(50.6%) of them respectively, moreover; Ductoplasty of the near multiple BDs was performed in 42(17.1%) of them, furthermore; the single, double and triple biliary anastomoses were done in 147(60%), 87(35.5%), and 11(4.5%) of them respectively. These anastomoses were classified into D-D(142 single, 80 double and 10 triple), HJ (single, 6 double and 1 triple) and D-D + HJ(one double) biliary reconstructions in 232(94.7%), 12(4.9%) and 1(0.4%) of patients respectively, moreover, prolene and PDS 6/0 sutures were used in 106 (43.3%) and 139(56.7%) of them respectively and external biliary stents were put in 224(91.4%) of them, the median actual graft weight and GRWR were 900 (range, 340–1250) gms and 1.1 (range, 0.6–1.7) respectively. Table 1.

The median cold ischemia (CIT), warm ischemia (WIT), and HA anastomotic times were 60 (range; 20–340) mins, 50 (range; 25–120)
The characteristics of recipients and their donors

| Category                                      | No (%)              |
|-----------------------------------------------|---------------------|
| BMI of the donor (Median(range))              | 26(18–35)           |
| Donor to recipient relation                   |                     |
| 1st degree                                     | 121(49.4%)          |
| 2nd degree                                     | 48(19.6%)           |
| 3rd degree                                     | 32(13.1%)           |
| 4th degree                                     | 16(6.5%)            |
| Unrelated                                      | 28(11.4%)           |
| Donor liver biopsy                            |                     |
| Normal                                         | 210(85.7%)          |
| Females                                        | 30(12.2%)           |
| Male                                           | 0(0%)               |
| MELD score (Median(range))                    | 167(15–34)          |
| CTP score                                      |                     |
| A                                              | 13(5.3%)            |
| B                                              | 64(26.1%)           |
| C                                              | 168(68.6%)          |
| Co-morbidity                                   | 64(26.1%)           |
| Pre LT PVT                                     | 38(15.5%)           |
| Pre LT PHN                                     | 224(91.4%)          |
| Bl. Group                                      |                     |
| Compatible                                     | 73(29.8%)           |
| Identical                                      | 172(70.2%)          |
| Graft type                                     |                     |
| RL-MHV                                         | 234(95.5%)          |
| RL + MHV                                       | 10(4.1%)            |
| Segments VI, VII                              | 1(0.4%)             |
| Liver graft HA NO                             |                     |
| 1                                              | 224(91.4%)          |
| 2                                              | 20(8.2%)            |
| 3                                              | 0(0%)               |
| HA anastomosis NO                             | 229(93.5%)          |
| 2                                              | 16(6.5%)            |
| Difficult HA anastomosis                      |                     |
| Liver graft BD NO                             | 5(2%)               |
| 1                                              | 121(49.4%)          |
| 2                                              | 100(40.8%)          |
| 3                                              | 20(8.2%)            |
| 4                                              | 6(2.4%)             |
| Ductoplasty of liver graft bile ducts         | 42(17.2%)           |
| Biliary anastomosis NO                        |                     |
| 1                                              | 147(60%)            |
| 2                                              | 87(35.5%)           |
| 3                                              | 11(4.5%)            |
| Biliary anastomosis type                      |                     |
| D-D                                           | 232(94.7%)          |
| HJ                                             | 12(4.9%)            |
| HJ + D-D                                      | 0(0%)               |
| Biliary anastomosis suture type               |                     |
| Prolene 6/0                                    | 106(43.3%)          |
| PDS 6/0                                       | 139(56.7%)          |
| External biliary stent                         | 224(91.4%)          |
| Actual graft weight(g) (Median(range))        | 900(1.1–1250)       |
| Actual GRWR (Median(range))                   | 1.10(0.6–1.7)       |
| CIT (min) (Median(range))                     | 60(20–340)          |
| WIT (min) (Median(range))                     | 50(25–120)          |
| HA anastomosis time (min) (Median(range))      | 60(11–290)          |
| Intraoperative blood transfusion (units) (Median(range)) | 40–40 |
| Intraoperative plasma transfusion(units) (Median(range)) | 50–53 |
| Operative time (hours) (Median(range))        | 12.5(7–29)          |
| Postoperative hospital stay(days) (Median(range)) | 17(1–120) |

Regimen including FK: 224(91.4%)
Regimen including MMF: 230(93.9%)
Regimen including Cyclosporine: 35(14.3%)
Regimen including Sirolimus: 33(13.5%)
Regimen including Everolimus: 20(8.2%)
Regimen including Simulect: 73(29.8%)
Post LT HAT/S: 34(13.9%)

BMI: Body mass index, PPF: Periportal fibrosis, MELD: Model for end-stage liver disease, CTP: Child-Turcotte-Pugh, Pre LT PVT: Pre liver transplantation portal vein thrombosis, PHN: portal hypertension, RI: Right lobe, MHV: Middle hepatic vein, HA: Hepatic artery, NO: Number, D-D: Duct to duct, HJ: Hepatocojunostomy, BD: Bile duct, PDS: Polydioxanone, GRWR: Graft recipient weight ratio, CIT: Cold ischemia time, WIT: Warm ischemia time, FK: Tacrolimus, MMF: Mycophenolate mofetil, HAT/S: Hepatic artery thrombosis or stenosis.

3.2. The original liver disease

The most frequent original liver diseases were hepatitis C virus (HCV)(51.8%), hepatocellular carcinoma(HCC)(31.8%) and cryptogenic liver cirrhosis(5.3%).

3.3. BCs and their management

One hundred fifty-five BCs affected 102 (41.6%) of our recipients (95 early (≤3months) and 60 late (>3months)). They were classified as 67/245(27.3%) early bile leak, 10/245(4.1%) early biliary stricture, 44/245 (17.9%) late biliary stricture, 4/245(1.6%) early cholangitis, 10/245(4.1%) late cholangitis, 14/245(5.7%) early biloma, and 6/245 (2.4%) late cholangitic abscesses.

Regarding early bile leaks, they affected 27.3% of our patients at a median of 0.5 (range; 0–3 months) and 60 late (≥3 months). They were classified as 67/245(27.3%) early bile leak, 10/245(4.1%) early biliary stricture, 44/245 (17.9%) late biliary stricture, 4/245(1.6%) early cholangitis, 10/245(4.1%) late cholangitis, 14/245(5.7%) early biloma, and 6/245 (2.4%) late cholangitic abscesses.

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3.4. Liver regeneration

The original liver disease.

| Category                                      | No (%)              |
|-----------------------------------------------|---------------------|
| Regimen including FK:                         | 224(91.4%)          |
| Regimen including MMF:                        | 230(93.9%)          |
| Regimen including Cyclosporine:               | 35(14.3%)           |
| Regimen including Sirolimus:                  | 33(13.5%)           |
| Regimen including Everolimus:                 | 20(8.2%)            |
| Regimen including Simulect:                   | 73(29.8%)           |
| Post LT HAT/S:                                | 34(13.9%)           |

HCV: Hepatitis C virus, HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus, AIH: Autoimmune hepatitis, PBC: Primary biliary cirrhosis, PSC: Primary sclerosing cholangitis.
surgical drainage, external biliary diversion and HJ in 25, 54, 26, five, three and one of them respectively with favourable outcomes in 51 of them. Table 3.

All early biliary strictures that affected 4.1% of recipients occurred at the 2nd post LT month where Clavien grades III and V affected 7 and three of these strictures respectively. ERCP ± stent and HJ were the treatment options in two, five and two of them respectively with a successful outcome in two and three of the early cases respectively. The conservative treatment options were PTBD, ERCP ± stent and HJ in two, 43 and 13 of them respectively where recovery occurred in 39 of them. Table 3.

Early and late cholangitis affected 4(1.6%) and 10(4.1%) of our patients respectively at a median of 2(range, 1–2) months, and 4(range; 3–14.5) months respectively. Clavien grades II, III and V affected one, one and two of early cases respectively; however, three and seven of late cases had Clavien grades III and V respectively. The conservative treatment and ERCP ± stent were the treatment options in one and three of the early cases respectively; however, they were the treatment options in four and seven of the late cases respectively. The outcome was favourable in two and three of the early and late cases respectively. Table 3.

We had 14 cases of early bilomas that occurred at a median of 0.75 (range; 0.06–2) months post-transplant; Clavien grades II, III and V affected three, seven and four of them respectively. The conservative treatment, percutaneous drainage and ERCP ± stent were the treatment options in five, eleven and two of them respectively with favourable outcomes in 10 of them. Table 3.

Lastly, late cholangitic abscesses affected 6(2.4%) of our patients at a median of 4.5 (range; 3–7) months; they all were Clavien grades V. Regarding their treatment; the conservative treatment(antibiotics), percutaneous drainage and open surgical drainage were the management strategies in two, five and two of them respectively with unfortunately unfavorable outcome in all of them (N.B two of them had associated HAS managed by angiographic dilatation and stenting, however, one of them had associated HAT managed by angiographic thrombolytic therapy and stenting). Table 3.

3.4. Predictors of BCs

On univariate analysis, heavier recipient weight, multiple graft BDs, multiple biliary anastomoses and post-LT HAT/S were significant predictors of BCs, however, multiple biliary anastomoses and post LT HAT/ S were independent predictors of those complications on multivariate analysis. Table 4.

3.5. Predictors of biliary leaks

On univariate analysis, multiple graft BDs, multiple biliary anastomoses and post-LT HAT/S were significant predictors of biliary leaks, however, post-LT HAT/S was the only independent predictor of those complications on multivariate analysis. Table 5.

3.6. Predictors of biliary strictures

On univariate analysis, D-D biliary anastomosis, and post-LT HAT/S were significant predictors of biliary strictures, however, post-LT HAT/S was the only independent predictor of those complications on multivariate analysis. Table 6.

3.7. The outcome of patients

Our 6-months, 1-year, 3-year, 5-year, 10-year and 16-year graft survival were 167(68.2%), 159(64.9%), 150(61.2%), 149(60.8%),149

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### Table 3

| Category | Early bile leak | Early biliary stricture | Late biliary stricture | Early cholangitis | Late cholangitis | Early biloma | Late cholangitic abscesses | Total |
|----------|----------------|-------------------------|-----------------------|------------------|----------------|--------------|--------------------------|-------|
| No (% of total patient NO) | 67(27.3%) | 10(4.1%) | 44(17.9%) | 4(1.6%) | 10(4.1%) | 14(5.7%) | 6(2.4%) | 155 (63.3%) |
| Onset per months | Early(≤3months) | 67(27.3%) | 10(4.1%) | 0 | 4(1.6%) | 0 | 14(5.7%) | 0 |
| Late(>3months) | 0 | 0 | 44(17.9%) | 0 | 10(4.1%) | 0 | 6(2.4%) | 95(38.8%) |
| Median(Range) | 0.5(0.03–2) | 2(2–2) | 6(3.5–36) | 2(1–2) | 4(3–14.5) | 0.75 | (0.06–2) | 60(24.5%) |
| Clavien grade | II | 62(2.4%) | 0 | 0 | 1(0.4%) | 0 | 3(1.2%) | 0 |
| III | 45(18.4%) | 7(2.8%) | 39(15.9%) | 1(0.4%) | 3(1.2%) | 7(2.9%) | 0 | 104(41.1%) |
| IV | 16(6.5%) | 3(1.2%) | 5(2%) | 20(8.9%) | 7(2.9%) | 4(1.6%) | 6(2.4%) | 43(17.6%) |
| V | | | | | | | | |
| Treatment | *1- Conservative | 25(10.2%) | 0 | 0 | 1(0.4%) | 4(1.6%) | 5(2%) | 20(8.9%) | 37(15.1%) |
| 2- Intervention | Percutaneous drainage | 54(22%) | 0 | 0 | 0 | 0 | 11(4.5%) | 5(2%) | 70(28.6%) |
| PTBD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20(8.0%) |
| ERCP ± Stent | 26(10.6%) | 9(3.6%) | 43(17.5%) | 3(1.2%) | 7(2.9%) | 20(8.9%) | 0 | 88(35.9%) |
| Open surgical drainage | 5(2%) | 0 | 0 | 0 | 0 | 0 | 0 | 7(2.9%) |
| External biliary diversion | 3(1.2%) | 0 | 0 | 0 | 0 | 0 | 3(1.2%) |
| HJ | 10(4.0%) | 3(1.2%) | 13(5.3%) | 0 | 0 | 0 | 0 | 17(7%) |
| Treatment outcome | Recovery | 51(20.8%) | 7(2.8%) | 39(15.9%) | 20(8.9%) | 3(1.2%) | 10(4.1%) | 0 | 112 (45.7%) |
| No recovery | 16(6.5%) | 3(1.2%) | 5(2%) | 20(8.9%) | 7(2.9%) | 4(1.6%) | 6(2.4%) | 43(17.6%) | 60(24.5%) |

BCs: Biliary complications, NO: Number, PTBD: Percutaneous transhepatic biliary drainage, ERCP: Endoscopic retrograde cholangiopancreatography, HJ: Hepaticojejunostomy.* Conservative: Wait and see with medication therapy (ie antibiotics, IV fluids, electrolytes, etc); if succeeded OK but if failed proceed with intervention.
Table 4
Pre- and intra-operative variables as predictors of BCs.

| Category                      | BCs         | No BCs       | P-value Univariate analysis | P-value Multivariate analysis |
|-------------------------------|-------------|--------------|----------------------------|-------------------------------|
| Donor age                     | 27.1 ± 6.9  | 26.9 ± 5.9   | 0.9                         |                               |
| BMI of donor                  | 25.4 ± 3.1  | 25.6 ± 3.4   | 0.58                        |                               |
| Donor liver biopsy            | 0.05        | 0.06         |                             |                               |
| Normal                        | 81          | 129          | (79.4%)                     | (90.2%)                       |
| PPF                           | 15          | 9 (6.3%)     |                             |                               |
| Steatosis                     | 6 (5.9%)    | 5 (3.5%)     |                             |                               |
| Recipient age                 | 0.12        | 0.05         |                             |                               |
| Recipient weight(kg)          | 82.5 ± 7.7  | 79.2 ± 7.9   | 0.043                       | 0.13                          |
| Recipient gender              | 13.3 ± 11.4 | 13.4 ± 11.4  |                             |                               |
| Males                         | 94          | 121          | (92.2%)                     | (84.6%)                       |
| Females                       | 8(7.8%)     | 22           | (15.4%)                     |                               |
| Cholestatic or immunological  | 10(7%)      | 11(7%)       | 0.59                        |                               |
| 1 yr disease                  | MELD score  | 15.6 ± 3.9   | 16.6 ± 4.1                  | 0.06                          |
| CTP score                     | A           | 7(6.9%)      | 6(4.2%)                     | 0.56                          |
| B                             | 28          | 36           | (27.5%)                     | (25.2%)                       |
| C                             | 67          | 101          | (65.7%)                     | (70.6%)                       |
| Pre LT PVT                    | 11          | 27           | (10.8%)                     | (18.9%)                       |
| Pre LT PHN                    | 93          | 131          | (91.2%)                     | (91.6%)                       |
| BL Group                      | 27          | 46           | (26.5%)                     | (32.2%)                       |
| Identical                     | 75          | 97           | (73.5%)                     | (67.8%)                       |
| Graft type                    | RL-MHV      | 100          | 134                         | (99%)                         |
| RL + MHV                      | 2(2%)       | 8(5.6%)      |                             |                               |
| Segments VI, VII              | 0           | 1(0.7%)      |                             |                               |
| Difficult HA anastomosis      | 4(3.9%)     | 1(0.7%)      | 0.08                        |                               |
| Liver graft BD NO 1           | 44          | 77           | (43.1%)                     | (53.8%)                       |
| 2                             | 48          | 52           | (47.1%)                     | (36.4%)                       |
| 3                             | 46          | 52           | (65.9%)                     | (149.8%)                      |
| 4                             | 3(3.9%)     | 0            |                             |                               |
| Ductoplasty of liver graft BDs| 15          | 27           | 0.39                        |                               |
| Biliary anastomosis NO 1      | 52(51%)     | 95           | (66.4%)                     |                               |
| 2                             | 43          | 44           | (42.2%)                     | (30.8%)                       |
| 3                             | 46          | 52           | (65.9%)                     | (149.8%)                      |
| Biliary anastomosis type D-D  | 99          | 133          | 0.2                         |                               |
| HJ                            | 57(60.1%)   | 97(67.8%)    | (90.2%)                     | (84.6%)                       |
| Prolene 6/0                   | 53(52%)     | 86           | (60.1%)                     |                               |
| Actual graft weight (g)       | 882.4 ± 665.3 | 141.8 | 0.37                        |                               |
| Actual GRWR                    | 1.1 ± 0.2   | 1.1 ± 0.2    | 0.33                        |                               |
| CIT (min)                     | 69.9 ± 39.5 | 72.5 ± 51.2  | 0.65                        |                               |
| WIT (min)                     | 52.9 ± 17   | 51.2 ± 17    | 0.55                        |                               |
| HA anastomosis time (min)     | 72.5 ± 17   | 69 ± 17      | 0.37                        |                               |
| Intraoperative blood transfusion (units) | 5.1 ± 4.6 | 5.5 ± 6.7 | 0.55                        |                               |
| Intraoperative plasma transfusion (units) | 6.1 ± 6.5 | 6.9 ± 8.2 | 0.40                        |                               |
| Operative time (hours)        | 12.7 ± 3.2  | 12.4 ± 3.1   | 0.58                        |                               |
| Post LT HAT/S                 | 24          | 10(7%)       | 0.000                       | 0.005                         |

Table 4 (continued)

| Category                      | BCs         | No BCs       | P-value Univariate analysis | P-value Multivariate analysis |
|-------------------------------|-------------|--------------|----------------------------|-------------------------------|
| Biliary anastomosis suture type | Prolene 6/0 | 49(49%)      | 57                          |                               |
| PDS 6/0                       | 53(52%)     | 86           | (60.1%)                     |                               |
| External biliary stent        | 92          | 132          | 0.56                        |                               |
| Actual graft weight (g)       | 882.4 ± 665.3 | 141.8 | 0.37                        |                               |
| Actual GRWR                    | 1.1 ± 0.2   | 1.1 ± 0.2    | 0.33                        |                               |
| CIT (min)                     | 69.9 ± 39.5 | 72.5 ± 51.2  | 0.65                        |                               |
| WIT (min)                     | 52.9 ± 17   | 51.2 ± 17    | 0.55                        |                               |
| HA anastomosis time (min)     | 72.5 ± 17   | 69 ± 17      | 0.37                        |                               |
| Intraoperative blood transfusion (units) | 5.1 ± 4.6 | 5.5 ± 6.7 | 0.55                        |                               |
| Intraoperative plasma transfusion (units) | 6.1 ± 6.5 | 6.9 ± 8.2 | 0.40                        |                               |
| Operative time (hours)        | 12.7 ± 3.2  | 12.4 ± 3.1   | 0.58                        |                               |
| Post LT HAT/S                 | 24          | 10(7%)       | 0.000                       | 0.005                         |

BCs: Biliary complications, MELD: Model for end-stage liver disease, CTP: Child-Turcotte-Pugh, Pre LT PTV: Pre liver transplant PVT, Pre LT PHN: Pre liver transplantation portal hypertension, BMI: Body mass index, PPF: Peri-portal fibrosis, RL: Right lobe, MHV: Middle hepatic vein, HA, Hepatic artery, D-D: Duct to duct, HJ: Hepaticojejunostomy, NO: Number, BDs: Bile ducts, PDS: Polydioxanone, GRWR: Graft recipient weight ratio, CTO: Cold ischemia time, WIT: Warm ischemia time. HAT: Hepatic artery thrombosis or stenosis.

(60.8%), and 149(60.8%) respectively, however, the 6-months, 1-year, 3-year, 5-year, 10-year and 16-year patient survival were 171(69.8%), 164(66.9%), 152(62%),150(61.2%),149(60.8%), and 149(60.8%) respectively. The mortality reached 96(39.2%) mostly due to sepsis, bleeding and multi-organ failure (MOF). On the other hand, the biliary related mortality was 26(10.6%).Table 7.

3.8. BCs as predictors of outcome

The overall BCs were not significantly associated with graft or patient survival; however, recurrent cholangitis and multiple cholangitic hepatic abscesses were significant predictors of poor both graft and patient survival when using the fisher’s exact tests. However, the abscesses were the only significant predictors of poor survival when using the log-rank tests.Table 8, Fig. 6.

4. Discussion

BCs after LDLT; especially A-ARLLDLT are a common problem reaching up to 60% of recipients [3–11,19]. Their management should be through a multidisciplinary team of transplant surgeons, hepatogastroenterologists, and intervention radiologists [1,20]. In similar; they affected 102 (41.6%) of our patients and were treated with the aid of our multidisciplinary team (i.e. Our treatment approaches started with the conservative measures (wait and see), but if failed; ERCP for leaks or strictures and/or pigtail and/or open surgical drainage for leaks were tried; however if failed PTBD or lastly HJ were allowed).
Table 5
Predictors of biliary leaks.

| Category | Biliary leaks | No leaks | P-value | P-value |
|----------|---------------|----------|---------|---------|
|          | No (%)        | No (%)   | Univariate analysis | Multivariate analysis |
|          | (Mean ± SD)   | (Mean ± SD) |             |          |
| Liver graft HA NO |               |          |              |          |
| 1        | 58 (86.6%)   | 166 (93.3%) | 0.10     | 0.3     |
| 2        | 8 (11.5%)    | 12 (6.7%)  |          |         |
| 3        | 1 (1.5%)     | 0 (0%)     |          |         |
| Liver graft BD NO |               |          |              |          |
| 1        | 23 (34.3%)   | 98 (55.1%)  | 0.006    | 0.94    |
| 2        | 36 (52.7%)   | 64 (36%)   |          |         |
| 3        | 7 (5.75%)    | 15 (8.4%)   |          |         |
| 4        | 3 (4.5%)     | 1 (0.6%)    |          |         |
| Biliary anastomosis NO |             |          |              |          |
| 1        | 30 (44.8%)   | 117 (65.7%) | 0.005    | 0.14    |
| 2        | 31 (46.3%)   | 56 (31.5%)  |          |         |
| 3        | 6 (9%)       | 5 (2.8%)    |          |         |
| Biliary anastomosis suture type |          |          |              |          |
| Prolene 6/0 | 35 (52.2%)  | 71 (38.9%)  | 0.06     | 0.21    |
| PDS 6/0   | 32 (47.8%)   | 107 (60.1%) |          |         |
| Recipient weight (kg) | 82.6 ± 13.8 | 79.8 ± 11.7 | 0.10     | 0.22    |
| Intraoperative plasma transfusion (units) | 5.2 ± 5.6 | 7.1 ± 8.1 | 0.08     | 0.20    |
| Post LT HAT or HAS | 16 (23.9%)  | 18 (10.1%)  | 0.007    | 0.029   |

HA, Hepatic artery; NO: Number; BDs: Bile ducts; HAT/S: Hepatic artery thrombosis or stenosis.

Table 6
Predictors of biliary strictures.

| Category | Biliary strictures | No biliary strictures | P-value | P-value |
|----------|--------------------|-----------------------|---------|---------|
|          | No (%)             | No (%)                | Univariate analysis | Multivariate analysis |
|          | (Mean ± SD)        | (Mean ± SD)           |         |         |
| Ductoplasty of liver graft BDs |               |          |              |          |
| 5 (9.3%) | 37 (19.4%)         | 305 (90.6%)           | 0.057   | 0.1     |
| Biliary anastomosis type(excluding HJ + D-D) |   |          |              |          |
| D-D      | 54 (100%)          | 178 (93.7%)           | 0.046   | 1       |
| HJ       | 0 (126.3%)         | 0 (0%)                |          |         |
| WIT (min) | 55.2 ± 16.9       | 50.8 ± 16.6           | 0.09    | 0.1     |
| Bile leak | 20 (37%)            | 47 (24.6%)            | 0.053   | 0.1     |
| Post LT HAT/S | 14 (25.9%)    | 20 (10.5%)            | 0.005   | 0.02    |

D-D: Duct to duct; HJ: Hepaticojunostomy; BDs: Bile ducts; WIT: Warm ischemia time. HAT/S: Hepatic artery thrombosis or stenosis.

Bile leaks occur mostly during the 1st two months post LDLT and their rate may reach up to 37% of recipients [5,9,21], moreover, they may come from the anastomotic site, the cut surface of the liver graft or the graft cut surface (51.67%; 76%), the graft cut surface (16.67%; 24%), and the cystic duct stump (1.67%; 1.5%), and were treated conservatively (25.67%; 37%), by percutaneous drainage (54.67%; 81%), by ERCP ± Stenting (26.67%; 39%) and/or by surgery(surgical drainage, external biliary diversion and HJ) (9.67; 13%) with favourable outcomes in 51.67% of them.

Post-LDLT biliary strictures are a common catastrophe reaching up to

Table 7
Recipients’ outcome.

| Category | No (%) | P-value |
|----------|--------|---------|
|          | (Mean ± SD) |         |
| Graft survival | 149 (100%) | 0.005   |
| 6 months survival | 167 (68.2%) | 1.0      |
| 1-year survival | 159 (64.9%) | 0.01    |
| 3-year survival | 150 (61.2%) | 0.02    |
| 5-year survival | 149 (60.8%) | 0.03    |
| 10-year survival | 149 (60.8%) | 0.04    |
| 16-year survival | 149 (60.8%) | 0.05    |
| Graft survival per months Median (Range) | 31 (0.03–192) | 0.10    |
| Patient survival | 171 (69.8%) | 0.001   |
| 6 months survival | 164 (66.6%) | 0.01    |
| 1-year survival | 152 (62%)  | 0.02    |
| 3-year survival | 150 (61.2%) | 0.03    |
| 5-year survival | 149 (60.8%) | 0.04    |
| 10-year survival | 149 (60.8%) | 0.05    |
| 16-year survival | 149 (60.8%) | 0.06    |
| Patient survival per months Median (Range) | 34 (0.03–192) | 0.10    |
| Mortality | 96 (39.2%) | 0.01    |
| Main causes: |          |         |
| Sepsis | 36 (14.6%) | 0.001   |
| Biliary sepsis | 18 (7.3%) | 0.01    |
| Sepsis from pneumonia | 18 (7.3%) | 0.01    |
| Bleeding | 13 (5.3%) | 0.01    |
| MOF | 11 (4.5%) | 0.01    |
| HCC recurrence | 7 (2.8%) | 0.02    |
| HAT | 6 (2.4%) | 0.01    |
| ARDS | 4 (1.6%) | 0.01    |
| Graft failure | 4 (1.6%) | 0.01    |
| PVT | 4 (1.6%) | 0.01    |
| Renal impairment | 3 (1.2%) | 0.01    |
| SSFS | 3 (1.2%) | 0.01    |
| Chronic rejection | 2 (0.8%) | 0.01    |
| CMV infection | 1 (0.4%) | 0.01    |
| HAT + PVT | 1 (0.4%) | 0.01    |
| Ischemic reperfusion injury | 1 (0.4%) | 0.01    |
| Biliary related mortality | 26 (10.6%) | 0.01    |

MOF: Multiorgan failure. HCC: Hepatocellular carcinoma. HAT: Hepatic artery thrombosis. ARDS: Adult respiratory distress syndrome. PVT: Portal vein thrombosis. SSFS: Small for size syndrome. CMV: Cytomegalovirus.

Table 8
BCs as predictors of outcome.

| Category | No (%) | P-value |
|----------|--------|---------|
| Overall BCs | 58 (38.9%) | 0.01    |
| Bile leak | 39 (26.2%) | 0.01    |
| Bile stricture | 32 (21.5%) | 0.01    |
| Cholangitis | 4 (2.7%) | 0.01    |
| Biloma | 7 (4.7%) | 0.01    |
| Cholangitic abscesses | 0 (0.0%) | 0.01    |

BCs: Biliary complications.

[22-24], or the cystic duct stump [22,25] and can be managed conservatively [26] and/or by Percutaneous drainage [23,25,26], and/or by ERCP ± sphincterotomy ± stenting [5,22,23,25–27] and/or by re-operation [5,22,23–27]. Similarly, biliary leaks that affected 27.3% of our patients occurred during the 1st two post-transplant months median 0.5 (range, 0.03–2 months) from the anastomotic site (51.67%; 76%), the graft cut surface (16.67%; 24%), and the cystic duct stump (1.67%; 1.5%), and were treated conservatively (25.67%; 37%), by percutaneous drainage (54.67%; 81%), by ERCP ± Stenting (26.67%; 39%) and/or by surgery(surgical drainage, external biliary diversion and HJ) (9.67; 13%) with favourable outcomes in 51.67% of them.
40% of patients [2,3]. They are anastomotic-/non-anastomotic ones; moreover, they may be angulated, tortuous, twisted, fork-shaped, trident-shaped, multi-branched, long and/or complicated strictures leading to more challenging therapy [28–30]. However, they can be managed successfully by endoscopy (ERCP ± sphincterotomy ± balloon dilatation ± stenting) [5,7,9,11–13,21,23,27,30–34], by PTBD [2,7,9,11–13,21,23,31–33] and/or by surgery (HJ) [7,12,21,32,33]. In the same way, the post LT biliary strictures (early and/or late) that affected

Fig. 6. Kaplan-Meier survival curves. A: Biliary complications and graft survival (Log rank = 0.62). B- Biliary complications and patient survival (Log rank = 0.65). C- Cholangitis and graft survival (Log rank = 0.05). D- Cholangitis and patient survival (Log rank = 0.06). E- Cholangitic abscesses and graft survival (Log rank = 0.006). F- Cholangitic abscesses and patient survival (Log rank = 0.008).
46/54 (85.2%) of them.

Post-LDLT bilomas are the collected localized intra- or para-hepatic biliary leaks occurring from bile duct rupture and biliary extravasation into the hepatic parenchyma or the abdominal cavity that can be managed conservatively [1,35,36], by percutaneous pigtail drainage [1, 35–38] and/or by ERCP ± stenting [1,35,39,40]. Also, the bilomas that affected 14/54 (25.9%) of our recipients were managed conservatively (5/36), by percutaneous pigtail drainage (11/14; 79%) and/or by ERCP ± stenting (2/14; 14%) with effective treatment in 10/14 (71.4%) of them.

The pyogenic hepatic abscesses that develop after LT are catastrophic rare events occurring in a range of 1.4–8.9% of patients due to several reasons (i.e. biliary causes (obstruction, reconstruction, drainage procedures (ERCP, PTBD), instrumentation (stents), cholangitis, insected bilomas, etc), HA complications (HAT/S), immunosuppression, DM, etc) [41–44], however, they can be managed medically (antibiotics) [42, 44], by percutaneous drainage [42–44], and/or by open surgery [44, 45]. In the same line; the cholangitic abscesses that affected 2/46 patients of our recipients occurred at a median of 4.5 (range; 3–7) months after ERCP with stenting and after repeated attacks of cholangitis, also, they were significantly correlated with HAT/S (P = 0.037), moreover, they were associated with DM but without significance (p = 0.1); those abscesses were managed medically (2/6; 33.3%), by percutaneous pigtail drainage (5/6; 83.3%), and/or by open surgical drainage (2/6; 33.3%) but unfortunately with unfavorable outcome.

BCs after LDLT are related to different (recipient, donor, graft, operative and/or postoperative factors) [46]; moreover, some of those factors were mentioned in different works of literature (i.e. centre volume/expertise, multiple small and short bile ducts from aberrant biliary anatomy, the type and number of biliary anastomoses, ductal intimal damage, necrosis, or ischemia during donor and recipient operations, HAT/S, CIT, WIT, immunological issues, ABO incompatibility, infections, etc) [7,9,35,47]. In this work; we analyzed the effect of different pre-, intra-, and post-transplant variables on the occurrence of post LT BCs.

Multiple graft BDs were significant predictors of overall BCs and leaks in our work, also, they were significant predictors of biliary strictures in Na et al., 2014 [48] study. However, they were not predictors of stricture or leak in Arikan et al., 2019 [8], Kim et al., 2009 [18], or Jung et al., 2014 [49] studies.

Multiple biliary anastomoses were independent predictors of overall BCs and significant predictors of biliary leaks in our work; also, they were predictors of BCs in Ogiso et al., 2020 [19] study, however, they were not predictors of stricture or leak in Arikan et al., 2019 [8], Kim et al., 2009 [18], or Özçelik et al., 2021 [50] studies, and were not associated with biliary stricture in Na et al., 2014 [48] study.

Despite the literature debate regarding the ideal method of biliary reconstruction in LDLT (D-D Vs HJ); D-D reconstruction is the procedure of choice and this is due to several reasons (i.e. being easier, quicker, more anatomic and physiologic, preserves SOD, has eliminated bowel manipulation, and is easy for ERCP post LT) [6,18]. In similar, it was done in 95% of our recipients. However, it was a predictor of biliary stricture in comparison to HJ in ours, Saidi et al., 2009 [5] and Kawachi et al., 2002 [51] studies, conversely, HJ was a predictor of biliary stricture, however, compared to D-D reconstruction in Gunawan et al. 2011 [25] and Icoz et al., 2003 [38] studies. Also, it was a predictor of biliary leaks and overall BCs in comparison with D-D reconstruction with a T-tube in Kobayashi et al., 2009 [52] study. On the other hand, the type of biliary anastomosis was not associated with BCs in Arikan et al., 2019 [8], Na et al., 2020 [13], Ogiso et al., 2020 [19], Park et al., 2003 [24], Jung, et al., 2014 [49] or Ramacciato et al., 2006 [53] studies.

We used external biliary stents in most of our cases (91.4%) due to several reasons (i.e. to keep the biliary flow and minimize intraductal pressure in the swollen edematous anastomosis, to keep small biliary lumens open, for assessment of graft function according to early bile production, and for doing simple cholangiography in suspected BCs); however, they had no significant impact on our BCs rate. Similarly, they did not affect the biliary outcome in Özçelik et al., 2021 [50] study. In contrast, the none use of them was an independent predictor of BCs in Hong et al., 2018 [54] study.

We found an independent correlation between Post LT HAT/S and overall BCs, strictures and leaks; similarly, arterial complications were independent predictors of BCs in Reyes et al., 2020 [10] study, and HAT/S was a significant predictor of biliary stricture in Gunawan et al., 2011 [25] study. Also, there was a significant association between HAS and biliary stricture in Hann et al., 2020 [55] study. Conversely, HAT was not associated with biliary stricture in Na et al., 2014 [48] study, and HA complications were not predictors of BCs in Ogiso et al., 2020 [19] study.

In our work, and despite non-reaching statistical significance; the biliary stricture rate was higher among leak cases; also, bile leak was an independent predictor of biliary stricture in Na et al., 2014 [48] study. The overall BCs were not significantly associated with long-term graft or patient survival in ours or Cortez et al., 2020 [27] studies, however, those complications were significant predictors of poor long-term graft and patient survival in Rönnin et al., 2019 [56] work, they were also independent predictors of a poor patient but not graft survival in Matar et al., 2021 [57] study. Moreover, the non-resolved biliary complications were significantly associated with poor long-term graft survival in Ogiso et al., 2020 [19] study.

Post LT recurrent cholangitis and cholangitic abscesses were significant predictors of poor graft and patient survival in our work, also, Post LT pyogenic liver abscess was a predictor of poor patient survival in Czerwono et al., 2018 [41] study, Moreover, cholangitis was a cause of death in Barbaro et al., 2021 [58] recipients; in the same line, biliary sepsis from recurrent cholangitis and a liver abscess was a cause of death in Na et al., 2014 [48] study. Lastly, sepsis either from biliary or non-biliary causes was the main cause of death in our recipients, similarly, it was a cause of death in Na et al., 2020 [13] recipients. In conclusion: Multiple biliary anastomoses and post LT HAT/S lead to poor biliary outcomes, furthermore, cholangitis, cholangitic abscesses and sepsis lead to poor graft and patient outcomes, so proper management of those variables is mandatory to improve outcomes after A-ARLLDLT.

Ethical approval

The approval by National liver institute (IRB), Menoufiya university that was done retrospectively.

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Author contribution

Emad Hamdy Gad: Surgical procedures, study design, data collection, writing, analysis and publication.
Eslam Ayoup: Surgical procedures, data collection, and analysis.
Amr M. Aziz: Surgical procedures, and analysis.
Tarek Elhelwawy: Endoscopic procedures, and data collection.
Mohammed Al-sayed Abd-elsamee: Intervention radiology procedures, and data collection.
Ahmed Nabil Sallam: Surgical procedures, data collection, and analysis.
advisable to do further randomized prospective studies of the studied issues.

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The main limitation of the study is its retrospective nature; so, it is advisable to do further randomized prospective studies of the studied issues.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amssa.2022.103577.

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