Management of Five Hundred Patients With Gut Failure at a Single Center

Surgical Innovation Versus Transplantation With a Novel Predictive Model

Kareem M. Abu-Elmagd, MD, PhD, FACS,✉ Sherif R. Armanyous, MD,* Masato Fujiki, MD,* Neha R. Parekh, MS, RD, LD, CNSC,* Mohammed Osman, MD,* Marissa Scalish, MPAS, PA-C,* Elizabeth Newhouse, RN, MSN, CCTC,* Yasser Fouda, MD,* Elizabeth Lennon, MS, PA-C, RD,* Abdullah Shatnawei, MD,* Donald Kirby, MD,* Ezra Steiger, MD,* Ajai Khanna, MD,† Kadakkal Radhakrishnan, MBBS, MD,* Cristiano Quintini, MD,* Koji Hashimoto, MD,* Julie Barnes, PharmD, RPh,* and Guilherme Costa, MD, PhD**

Objective(s): To define the evolving role of integrative surgical management including transplantation for patients gut failure (GF).

Methods: A total of 500 patients with total parenteral nutrition-dependent catastrophic and chronic GF were referred for surgical intervention particularly transplantation and comprised the study population. With a mean age of 45 ± 17 years, 477 (95%) were adults and 23 (5%) were children. Management strategy was guided by clinical status, splanchnic organ functions, anatomy of residual gut, and cause of GF. Surgery was performed in 462 (92%) patients and 38 (8%) continued medical treatment. Definitive autologous gut reconstruction (AGR) was achievable in 378 (82%), primary transplant in 42 (9%), and AGR followed by transplant in 42 (9%). The 84 transplant recipients received 94 allografts; 67 (71%) liver-free and 27 (29%) liver-contained. The 420 AGR patients received a total of 790 reconstructive and remodeling procedures including primary reconstruction, interposition alimentary-conduits, intestinal/colonic lengthening, and reductive/decompressive surgery. Glucagon-like peptide-2 was used in 17 patients.

Results: Overall patient survival was 86% at 1-year and 68% at 5-years with restored nutritional autonomy (RNA) in 63% and 78%, respectively. Surgery achieved a 5-year survival of 70% with 82% RNA. AGR achieved better long-term survival and transplantation better ($P = 0.03$) re-established nutritional autonomy. Both AGR and transplant were cost effective and quality of life better improved after AGR. A model to predict RNA after AGR was developed computing anatomy of reconstructed gut, total parenteral nutrition requirements, cause of GF, and serum bilirubin.

Conclusions: Surgical integration is an effective management strategy for GF. Further progress is foreseen with the herein-described novel techniques and established RNA predictive model.

Keywords: graft versus host disease (GVHD), immunosuppressive regimens-induction, intestinal (allograft function)/dysfunction, intestinal failure/injury, nutritional autonomy, patient survival, predictive model, quality of life

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The gut plays a major role in the whole-body energy equilibrium and human wellness.[1–3] Disruption of gut homeostasis often leads to loss of energy balance with development of life-threatening complications.[4] Catastrophic surgical complications, splanchnic vascular occlusion, and end-stage gastrointestinal disorders commonly cause gut failure (GF) with the need for total parenteral nutrition (TPN).[4–14]

In the 1960s, TPN was introduced as the only life-saving treatment for patients with GF.[15] In 1980, longitudinal bowel lengthening was described for short gut syndrome patients to enhance gut adaptation and reduce risk of bacterial overgrowth.[16] A decade later, gut transplantation was established to rescue patients who can no longer be maintained on TPN.[17] Despite cumulative improvement in outcome, transplantation continued to have restricted indications and limited worldwide availability.[18,19]

With the inherent therapeutic limitations of both TPN therapy and transplantation, the concept of gut rehabilitation was introduced and gradually evolved utilizing novel treatment modalities.[18,20–24] Continual evolution of such a comprehensive approach has the potential to optimize patient care with better outcome including the value of healthcare. These noble goals are essential to further advance the field and sustain affordability of rescuing these complex patients.

With a few scattered small published series, this is the largest single-center study that comprehensively addresses the integrative management of patients with a wide variety of GF.[23–26] Innovative autologous and transplant surgical techniques were introduced in the milieu of preserved splanchnic organ functions, residual gut anatomy, and cause of GF. The primary therapeutic end-points were analyzed and independent predictors were computed including severity of nutritional insufficiency to establish a novel model that calculates the probability of retrieving nutritional autonomy.

METHODS

Study Design

The study was conceptualized since the inception of Cleveland Clinic-Center for Gut Rehabilitation and Transplantation (CGRT) on August 1, 2012. An integrative approach was envisioned for management of TPN-dependent GF patients. After Institutional Review Board approval, data were retrieved utilizing the electronic database and chart review. The nationally shared medical records were accessed and telephone interviews were conducted for a complete and updated follow-up.

Definitions

GF is defined as reduction of the functioning cell mass and/or absorptive capacity with the need for TPN.[27] Catastrophic GF means loss of nutritional autonomy due to major surgical complications or acute splanchnic vascular events that resulted in prolonged hospitalization until time of referral. Chronic GF identifies patients with intrinsic gut disorders or complex abdominal pathology requiring

From the *Cleveland Clinic Foundation, Cleveland, OH; and †University of Pittsburgh Medical Center, Pittsburgh, PA.
✉abuelmk@ccf.org.
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long-term TPN. Disconnected gut indicates segmental stapling, fistulae, stoma, or external venting. Short gut syndrome (SGS) patients are those with ≤ 200 cm residual intestine and ultra-SGS implies total enterectomy. GF is classified into surgical (anatomic), mucosal (endodermal), and neuromuscular (ectodermal/mesodermal). Surgical GF includes a variety of correctable etiologies including altered anatomy and adhesive/malignant obstruction. The main stay of mucosal GF is impaired enterocyte functions with Crohn's disease, irradiation, and congenital enteropathy. The hallmark of neuromuscular GF is congenital and acquired motility disorders.

Autologous gut reconstruction (AGR) defines different reconstructive and remodeling procedures to reestablish gut continuity, restore normal alimentary flow, and modulate transit time. Transplant nomenclature is defined elsewhere.[28,29]

Study Population

Between August 1, 2012 and February 15, 2019, a total of 750 patients were referred with refractory gut disorders and complex abdominal pathology. Of these, 500 (67%) suffered catastrophic or chronic GF and comprised the study population. The remaining 250 patients did not require TPN therapy and were excluded.

Catastrophic GF was documented in 202 (40%) patients who were transferred to our facility after 6 weeks to 2 years of hospitalization at the referring center. The remaining 298 (60%) failed disease-specific management and were evaluated as outpatients. The geographic referral was regional (46%), national (44%), and international (10%). Full clinical features are summarized in Table 1 with yearly activity illustrated in Supplementary Figure-1, http://links.lww.com/SLA/B735.

TABLE 1. Clinical Features of the Total Population and According to Type of Gut Failure (GF)

		Type of Gut Failure (GF)			
	Total	**Surgical**	**Mucosal**	**NeuroMuscular**	***P***
No. patients	500	301 (60)	92 (19)	107 (21)	
Age (mean ± SD, yr)	45 ± 17	48 ± 17	48 ± 18	38 ± 14	**<0.001**
Adults	477 (95)	287 (95)	87 (95)	103 (96)	
Children	23 (5)	14 (5)	5 (5)	4 (4)	
Sex (female: male)	1.7:1	1.3:1	1.3:1	6.6:1	**<0.001**
Race/ethnicity					**0.003**
White	390 (78)	217 (72)	81 (88)	92 (86)	
African American	49 (10)	39 (13)	3 (3)	7 (7)	
Others	61 (12)	45 (15)	8 (9)	8 (7)	
Geographic distribution					
Regional (Ohio and Pennsylvania)	230 (46)	152 (51)	38 (41)	40 (37)	**0.01**
National (USA)	219 (44)	113 (38)	46 (50)	60 (56)	
International	51 (10)	36 (22)	8 (9)	7 (7)	
Hospital to hospital transfer	202 (40)	149 (50)	29 (32)	24 (22)	**<0.001**
Prior abdominal surgery (mean ± SD)	5 ± 5	5 ± 4	6 ± 6	5 ± 5	0.27
Disease duration (year, median [IQR])	5 [1– 12]	2 [1– 5]	14 [4– 29]	9 [5– 14]	**<0.001**
History of malignancy (%)	113 (23)	73 (24)	29 (32)	11 (10)	**0.001**
History of abdominal irradiation	19 (4)	0 (0)	19 (20)	0 (0)	**<0.001**
Total parenteral nutrition (TPN)					
Duration (mo, median [IQR])	12 [3–27]	9 [2–18]	23 [9–49]	15 [6–39]	**<0. 001**
Volume (mL/d)	2370 ± 768	2436 ± 776	2428 ± 864	2111 ± 585	**0.003**
kcal/kg/d	26 ± 13	26 ± 12	26 ± 13	25 ± 13	0.56
Body mass index (kg/m^2) (mean ± SD)	25 ± 6	25 ± 7	23 (6)	24 ± 6	**0.018**
Short gut syndrome (≤ 200 cm)	295 (59)	203 (67)	75 (82)	17 (16)	**<0.001**
Ultra-short gut syndrome (0 cm)	71 (14)	53 (18)	10 (11)	8 (8)	**0.022**
Remaining intestine (cm, mean ± SD)	63 ± 61	57 ± 58	81 ± 64	53 ± 70	**0.014**
Plasma citrulline (n)	268	134	57	77	
Level (mean ± SD, umol/L)	22 ± 14	20 ± 15	22 ± 14	24 ± 11	**0.012**
Disconnected gut (fistulae ± stoma)	358 (72)	246 (82)	70 (76)	42 (39)	**<0.001**
Reduced gut (stomach/duodenum/colon)	400 (80)	251 (83)	80 (87)	69 (65)	**<0.001**
Intact ileocecal valve	176 (35)	115 (38)	19 (21)	42 (39)	**0.005**
Portomesenteric venous thrombosis	24 (5)	20 (7)	4 (4)	0 (0)	**0.008**
Thrombophilia	200 (40)	129 (43)	35 (38)	36 (34)	0.114
Serum bilirubin (mg/dL, mean [range])	0.5 [0.3 –1]	0.5 [0.1–52]	o.7 [0.2–53]	0.4 [0.1–5.7]	**<0.001**
Liver Pathology	306	185	52	69	
Steatosis (≥ 50%)	27 (9)	17 (9)	3 (6)	7 (10)	0.747
Fibrosis (1–3)	119 (40)	78 (42)	22 (42)	19 (28)	0.235
Cirrhosis	15 (5)	11 (6)	3 (6)	1 (1)	0.332
Serum creatinine (mg/dL)	0.9 ± 0.5	0.9 ± 0.6	0.9 ± 0.4	0.7 ± 0.2	0.103
Axis I–II psychiatric disorders	281 (56)	145 (48)	57 (62)	79 (74)	**<0.001**
Preoperative comorbidity (ASA IV–V class)	148 (33)	89 (32)	34 (43)	25 (28)	0.12
Surgical management*	462 (93)	286 (95)	85 (93)	91 (85)	0.11
Gut Transplant	84 (17)	34 (12)	26 (31)	24 (26)	**<0.001**
GLP-2 treatment	17 (3)	10 (3)	5 (5)	2 (2)	0.371
Overall survival	388 (78)	225 (75)	71 (77)	92 (86)	0.057
Overall TPN-free survival	267 (69)	169 (75)	50 (70)	48 (52)	**0.005**
Follow-up (mo, mean ± SD)	30 ± 23	32 ± 24	27 ± 23	27 ± 19	**0.051**

*Forty-two patients were transplanted after autologous reconstruction.

Evaluation

Catastrophic GF patients who were referred with hemodynamic instability and respiratory failure were received at the intensive care unit and prompt surgical intervention was initiated when indicated. Stable patients were admitted to the surgical ward and received inpatient care until surgery particularly those with extensive abdominal wall disruption, complex enteroatmospheric fistulae and recurrent sepsis (Supplementary Figure-2, http://links.lww.com/SLA/B735). Most of the chronic GF cases were evaluated as outpatients.

Initial evaluation was directed toward assessment of nutritional status, residual gut anatomy, underlying pathology, associated organ dysfunctions, and coexisting morbidities with special focus on candidacy for AGR or transplantation. Targeted clinical, laboratory, radiologic, endoscopic, and histopathologic examinations were established including plasma citrulline levels in selected cases. Full transplant work-up was done only for patients who required organ replacement.[30]

Management Strategy

Integrative surgical and medical management was applied with an algorithm that was streamlined by detailed clinical information, status of native liver, structure of residual gut, and cause of GF (Fig. 1). Catastrophic GF patients with open abdomen, nonviable residual gut, and disrupted surgical anastomoses underwent lifesaving surgery as definitive treatment or bridge to transplantation. Clinically stable patients underwent elective AGR or completed the transplant evaluation.

With preserved hepatic functions, patients with reconstructable anatomy and residual gut function underwent organ-sparing AGR with the aim of restoring natural alimentary flow. The procedures were commonly used as a definitive therapy. In selected patients, AGR was used to salvage transplant candidacy and reduce type of allograft. Primary, simultaneous, or sequential serial transverse enteroplasty (STEP) along with the newly described serial transverse coloplasty (STCP) was used for the SGS patients to slow transit time and reduce bacterial overgrowth. The trifecta procedure was another novel operation that was initially introduced to the neuromuscular GF patients as a bridge to transplantation. The procedure includes subtotal colectomy, pyloroplasty, and chimney ileostomy to enhance oral tolerance, modify transit time, and ameliorate bacterial overgrowth.

Transplantation was indicated from the outset for patients with combined hepatoenteric failure and those who can no longer be maintained on TPN particularly those with ultra-SGS, unreconstructable gut, congenital enteropathy, and unsuccessful prior gut

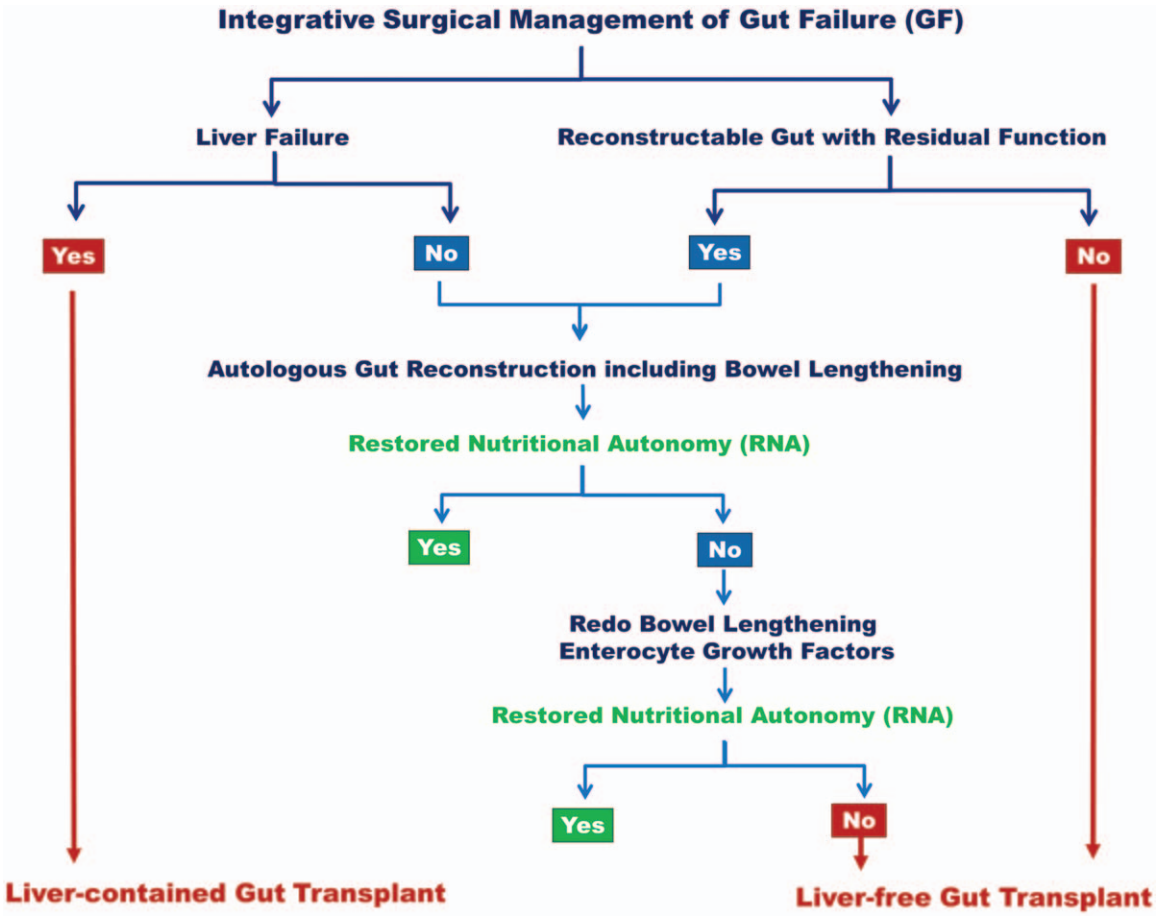

FIGURE 1. Surgical algorithm for management of patients with gut failure. Comprehensive medical management including enterocyte growth factors was continued for poor surgical/transplant candidates and those who were denied financial coverage or elected to defer surgery. The trifecta procedure was exclusively used for the neuromuscular GF patients.

transplantation. The procedure was also used to rescue AGR failure patients. The type of allograft was primarily dictated by the functional anatomy of solid abdominal organs and residual gut.

Comprehensive medical management including enterocyte growth factors was offered for poor surgical/transplant candidates and those who were denied financial coverage or initially elected not to proceed with surgery.

Case Material

The study included 477 (95%) adults and 23 (5%) children with an age ranging from 6 months to 86 years. Leading causes of surgical GF were complex and surgical mesh associated enteric fistulae (31%), vascular thrombosis (26%), and bariatric surgery (24%). History of thoracic/non-intestinal abdominal organ transplant and complicated Whipple/total pancreatectomy with auto-islet transplant was documented in a total of 10% of the surgical GF patients. The underlying mucosal disorders were Crohn's disease (58%), radiation enteritis (21%), vasculopathy (13%), and congenital enteropathy (5%) with 2 examples of RFX6 and TTC7A genetic mutations.

A total of 462 (92%) patients received surgical treatment; definitive AGR in 378 (82%), primary transplant in 42 (9%), and AGR followed by transplant in 42 (9%). With a time interval of 2 to 43 (mean: 14 ± 10) months, transplant was required after AGR in patients with ultra-SGS (n = 16), $\leq$ 50 cm jejunum with end stoma (n = 8), and residual desmoids (n = 5). The remaining 13 patients continued to experience GF after trifecta (n = 8) and sleeve gastroplasty (n = 4) or STEP (n = 1) in SGS patients. Clinical features of the AGR total patients are summarized in Table 2.

The 84 (17%) transplant recipients received 94 allografts (Table 3). Eight failed prior gut transplant at another center and 1 was HIV positive. The 67 (71%) liver-free allografts were intestine (n = 56), intestine-pancreas (n = 3), and modified multivisceral (n = 8). The 27 (29%) liver-contained allografts were liver-intestine (n = 9) and full multivisceral (n = 18). Donor colon was included in 8 and kidney in 2 allografts. All donors were deceased and ABO identical.

The 38 (8%) patients who continued TPN therapy received comprehensive nutritional care with glucagon-like peptide (GLP-2) treatment for 6 SGS patients. With the exception of 6 (16%) currently listed patients, 23 (65%) were not suitable surgical candidates

TABLE 2. Clinical Features and Surgical Anatomy of the Four-Hundred Twenty Patients Who Underwent Autologous Gut Reconstruction (AGR)

	Total No.	AGR-only	AGR Followed by Gut Transplant	*P*
No. patients	420	378 (90)	42 (10)	
Age (mean ± SD, yr)	46 ± 16	48 ± 16	42 ± 16	**0.038**
Children/Adults	14/406	11/367	3/39	
Sex (female: male)	1.8:1	1.8:1	1.5:1	0.685
Cause of gut failure				
Surgical	274 (65)	252 (67)	22 (52)	
Neuromuscular	78 (19)	67 (18)	11 (26)	0.180
Mucosal	68 (16)	59 (16)	9 (21)	
Hospital to hospital transfer	191 (46)	166 (44)	25 (60)	0.078
Prior abdominal surgery (mean ± SD)	4 (0–40)	5 (0–40)	6 (2–25)	0.27
Disease duration (yr, median [IQR])	4 [1–12]	3 [1–10]	11 [3–17]	**0.04**
History of malignancy	105 (25)	96 (25)	9 (21)	0.707
History of abdominal irradiation	18 (4)	17 (5)	1 (2)	0.5
Total parenteral nutrition (TPN)				
Duration (mo, median [IQR])	11 [2–25]	10 [2–23]	20 [8–36]	**0.03**
Volume (mL/d, mean ± SD)	2365 ± 747	2322 ± 722	2896 ± 849	**<0.001**
kcal/kg/d	25 ± 11	25 ± 11	30 ± 15	0.077
Body mass index (kg/m^2) (mean ± SD)	25 ± 6	25 ± 6	24 ± 5	0.614
Short gut syndrome ($\leq$ 200 cm)	246 (59)	212 (56)	34 (81)	**0.0019**
Ultra-short gut syndrome (0 cm)	52 (12)	36 (16)	16 (38)	**<0.001**
Remaining intestine (cm)	87 ± 56	94 ± 54	23 ± 14	**<0.001**
Plasma citrulline (n)	213	182	31	
Level (umol/L)	22 ± 13	24 ± 13	13 ± 13	**<0.001**
Disconnected gut (fistulae ± stoma)	334 (80)	301 (80)	33 (79)	0.8
Reduced gastrointestinal organs				
Stomach	113 (27)	103 (27)	10 (24)	0.6
Duodenum	74 (18)	60 (16)	14 (33)	**0.05**
Pancreas	19 (4)	18 (5)	1 (2)	0.09
Colon	267 (64)	228 (60)	39 (92)	**<0.001**
Intact ileocecal valve	166 (40)	163 (43)	3 (7)	**<0.001**
Diffuse portomesenteric venous thrombosis	21 (5)	18 (5)	3 (7)	0.455
Thrombophilia	173 (41)	151 (40)	22 (54)	0.130
Serum bilirubin (mg/dL)	0.9 ± 0.7	0.9 ± 0.6	1.2 ± 1.3	0.17
Liver pathology	266	228	128	
Steatosis ($\geq$50%)	20 (8)	18 (8)	2 (5)	0.748
Fibrosis (1–3)	100 (38)	80 (35)	20 (53)	**0.008**
Cirrhosis	12 (5)	8 (4)	4 (11)	0.3
Serum creatinine (mg/dL)	0.9 ± 0.5	0.9 ± 0.5	0.7 ± 0.08	0.065
Axis I–II psychiatric disorders	222 (53)	190 (50)	32 (76)	**<0.001**
Preoperative comorbidity (ASA class)				
II–III	283 (70)	267 (73)	16 (38)	**<0.001**
IV–V	123 (30)	97 (27)	26 (62)	

TABLE 3. Clinical Features and Outcome Among the Gut Transplant Recipients and According to Type of Allograft

	Total	Liver-free	Liver-contained	*P*
Number of recipients	84	62 (74)	22 (26)	
Number of allografts	94	67 (71)	27 (29)	
Recipient age (mean ± SD, yr)	39 ± 18	38 ± 16	37 ± 23	0.7
Children/adult	8/76	4/58	4/18	**0.023**
Recipient Sex (female: male)	1.6: 1	2.4: 1	0.6: 1	**0.004**
TPN duration (mean ± SD, mo)	66 ± 45	56 ± 45	53 ± 44	0.9
Disease duration (mean ± SD, yr)	14 ± 14	14 ± 13	18 ± 15	0.8
Prior abdominal surgery	6 ± 5	6 ± 5	6 ± 6	0.7
Body mass index (kg/m^2)	23 ± 5	24 ± 5	23 ± 6	0.4
Type of gut failure				
Surgical	34 (40)	23 (37)	11 (50)	
Neuromuscular	24 (29)	22 (35)	2 (9)	0.06
Mucosal	26 (31)	17 (28)	9 (41)	
Short gut syndrome (SGS, ≤ 200 cm)	64 (76)	47 (76)	17 (77)	
Ultra-short gut syndrome (0 cm)	30 (36)	23 (37)	7 (33)	0.6
Length of residual intestine (cm)	26 ± 17	26 ± 16	29 ± 20	
Portomesenteric venous thrombosis	6 (7)	1 (2)	5 (23)	**0.002**
Serum bilirubin (mg/dL)	10 ± 4	3 ± 1	17 ± 11	**0.001**
Pretransplant autologous reconstruction	42 (50)	31 (50)	11 (50)	0.9
Positive T/B cell cross-match	22 (26)	15 (24)	7 ((31)	0.6
Splenectomy	16 (19)	4 (6)	12 (55)	**0.001**
Recipient pretreatment (primary graft)	60 (71)	58 (94)	2 (9)	**<0.001**
Campath-1H	57 (95)	55 (95)	2 (100)	
Thymoglobulin	3 (5)	3 (5)	0 (0)	
Operative data				
Portal drainage of liver-free allograft	NA	33 (49)	NA	
Cold ischemia time (h)	8 ± 1	7 ± 1	9 ± 1	0.07
Operative time (h)	12 ± 2	11 ± 2	14 ± 3	**0.04**
Total blood loss (unit)	15 ± 9	10 ± 8	19 ± 15	**0.03**
Length of hospital stay (mean ± SD, d)	46 ± 36	38 ± 3	69 ± 39	**0.005**
Graft loss	42 (45)	28 (42)	14 (52)	0.374
Death	26 (62)	14 (50)	12 (85)	**0.024**
Graft failure	16 (38)	14 (50)	2 (15)	**0.025**
Lymphoproliferative disorder (PTLD)	5 (6)	5 (8)	0 (0)	**0.001**
Graft versus host disease (GVHD)	4 (5)	1 (2)	3 (14)	**0.002**
Survival	54 (64)	41 (66)	13 (59)	0.4
Total parenteral nutrition-free survivor	45 (83)	35 (85)	10 (77)	0.06

because of high comorbidity index including history of aggressive cancer (n = 10), psychosocial barriers (n = 9), and economic hardship (n = 4). The remaining 9 (24%) continued to defer surgery or were denied financial coverage.

SURGICAL PROCEDURES

Autologous Gut Reconstruction

All operations were done with open techniques. Patients with hostile abdomen underwent external ureteric stent placement. The mesenteric leaves guided surgical orientation and dissection was with thermal hemostatic devices. All reconstructive techniques were gut-sparing with careful preservation of the segmental blood supply. Re-establishment of the natural alimentary flow was achievable in most cases with utilization of visceral conduits when indicated. All anastomoses were tension-free and hand-sewn in 2 layers. Cholecystectomy was required for most patients and pyloroplasty was performed with foregut reconstructions. Infected surgical mesh was removed and component separation was performed in noninfected patients.

A total of 790 (1.9/patient) reconstructive/remodeling procedures were performed; 654 primary reconstructions, 18 alimentary conduits, 84 bowel lengthening, and 34 trifecta (Table 4). Additional procedures included end-stoma (n = 89) and hernia repair (n = 64). All were performed simultaneously or alone with the exception of 10 bowel lengthening that were performed after the initial AGR. The reconstructive procedures were primarily mid and foregut (Fig. 2A) with few examples of concomitant portal hypertensive surgery (supplementary Figure-3, http://links.lww.com/SLA/B735).

With massive gut loss, different life-saving reconstructive techniques were used to rescue transplant candidacy and reduce type of allograft (Fig. 2B). The residual colon is anastomosed to leaking upper gut visceral organs and a simple or Roux-en Y reconstruction was guided by length of residual colon.

A total of 18 alimentary conduits were used; 10 colonic and 8 jejunal. The colonic conduits restored the flow between cervical esophagus and stomach or jejunum in 6 patients with failed gastric pull-up for congenital (n = 2), and acquired (n = 4) esophageal pathology (Fig. 2C). The remaining 4 restored the infra-diaphragmatic foregut continuity with the repair of a major duodenal defect in a Crohn's disease SGS patient (Fig. 2D, a and b). The jejunal conduits reestablished the alimentary flow in patients with resected stomach and SGS with creation of a neo-stomach (Fig. 2D, c and d).

STEP was modified by over sewing staple lines (Fig. 3A). It was performed in 68 (14%) patients; once in 53, twice in 13, and 3 times in 2 with a total of 85 operations. It was concomitant with AGR in 39 (57%) and the remaining 29 (43%) patients had the procedure alone (n = 19) or after AGR (n = 10) with a mean time interval of 16 ± 12 (range: 4–40) months. One of these patients had intestine-only transplant and developed SGS after partial allograft loss due to

TABLE 4. Surgical Techniques, Complications, and Outcome in Patients Who Underwent Autologous Gut Reconstruction (AGR)

Primary	AGR-only	AGR Followed by Gut Transplant	Total
No. of patients (%)	378 (90)	42 (10)	420
Primary autologous reconstruction (total no.)	628	26	654
Esophageal	15 (4)	1 (2)	16 (4)
Gastric	165 (44)	8 (19)	173 (41)
Duodenal	82 (22)	12 (29)	94 (22)
Enteric	295 (78)	5 (12)	300 (71)
Colonic	71 19)	0 (0)	71 (17)
Interposition alimentary conduit (total no.)	18 (5)	0	18 (4)
Colon	10	0	10
Jejunum	8	0	8
Intestinal and colonic lengthening			
Number of patients	66 (17)	1 (2)	67* (16)
STEP/STCP	66/12	1/0	67*/12
Number of procedures	83	1	84
Number of cuts (range)	2 – 36	3	2 – 36
Gained length (mean ± SD, cm)	21 ± 13	5	21 ± 14
Trifecta procedure	32 (8)	2 (5)	34 (8)
End stoma	65 (17)	24 (57)	89 (21)
Concomitant ventral hernia repair	64 (17)	0 (0)	64 (15)
Operative time (h)	8 ± 3	9 ± 3	8 ± 3
Total blood loss (unit)	2 ± 1	3 ± 1	2 ± 1
Clavien-Dindo grades (III-b–V)	69 (18)	3 (7)	72 (17)
III-b	54 (14)	2 (5)	56 (13)
IV	8 (2)	1 (2)	9 (2)
V	7 (2)	0 (0)	7 (2)
Length of hospital stay (mean ± SD, d)	28 ± 25	18 ± 10	26 ± 23
Survival	308 (82)	29 (69)	337 (81)
Total parenteral nutrition-free survival	219 (71)	26 (90)	245 (73)

*An additional patient had STEP of the intestinal allograft.
Trifecta indicates subtotal colectomy, pyloroplasty and chimney ileostomy. STEP indicates serial transverse enteroplasty; STCP, serial transverse coloplasty.

rejection. Along with STEP, STCP was safely performed in 12 patients with preservation of the marginal artery of Drummond and avoidance of the watershed areas (Fig. 3B). Recruitment of healthy intestinal segments was accomplished in 10 SGS patients with prior segmental bypass or dysfunctional anastomoses (Fig. 3C). Trifecta (Fig. 3D) was performed in 34 of the 78 surgically treated neuromuscular GF patients with reductive/decompressive surgery in the remaining 44.

Transplantation

A few modifications were introduced to the recipient operation.[31,32] Preservation of native spleen and pancreaticoduodenal complex was feasible with 6 (75%) modified (Fig. 4A) and 3 (17%) full multivisceral (Fig. 4B) transplants. Meanwhile, in-situ native jejunal or colonic segments were used to reestablish upper gut continuity (Fig. 4C, D) with 4 recipients receiving a donor colon pull-through operation to restore continuity of hindgut (Fig. 4E). With these modifications, more native structures were preserved and less donor organs were needed with safe surgical reconstruction.

Postoperative Care

A stepwise enteral feeding with gradual TPN withdrawal was initiated early after surgery. Infectious prophylaxis was more inclusive with transplant and active treatment was frequently required after AGR due to multiresistant intra-abdominal microbial infections. Short-term thromboprophylaxis was universal and life-long anticoagulation was needed for thrombophilic individuals. Crohn's disease patients continued targeted therapy. Prokinetic and antidiarrheal drugs were required for dysmotility and SGS patients with periodic treatment of bacterial overgrowth. GLP-2 was given to 11 AGR-SGS patients who failed TPN weaning.[33]

The complexity of posttransplant management stemmed from the high immunogenicity of the intestinal allograft.[34,35] Immunosuppression was tacrolimus-steroid based with 60 (71%) patients pretreated with a single dose of campath-1H (30 mg) or rATG (5 mg/kg) (Table 3). IVIG (2 g/kg) and Bortezomib (1.3 mg/m^2) or Rituximab (375 mg/m^2) were given to 12 presensitized patients. Immunologic monitoring included early diagnosis and treatment of rejection and graft versus host disease (GVHD).[35] Posttransplant lymphoproliferative disorders and cytomegalovirus infections were diagnosed and treated as previously described.[32]

Long-term follow-up included regular visits with yearly evaluation of different nutritional, metabolic, and skeletal health indices. Transplant recipients were followed more closely with frequent assessment of allograft functions.

Quality of Life Assessment

The evaluation process included physical, neurological, and psychological examination. Karnofsky/Lansky scale was used to assess physical performance. Number of hospital readmissions, changes in gastrointestinal symptoms, number of medications, and new onset comorbidities were used as surrogate markers of global health.

Neuropsychiatric and socioeconomic status was assessed by qualified mental health professionals. The American Psychiatric Association DSM-V multi-axial system was used to classify

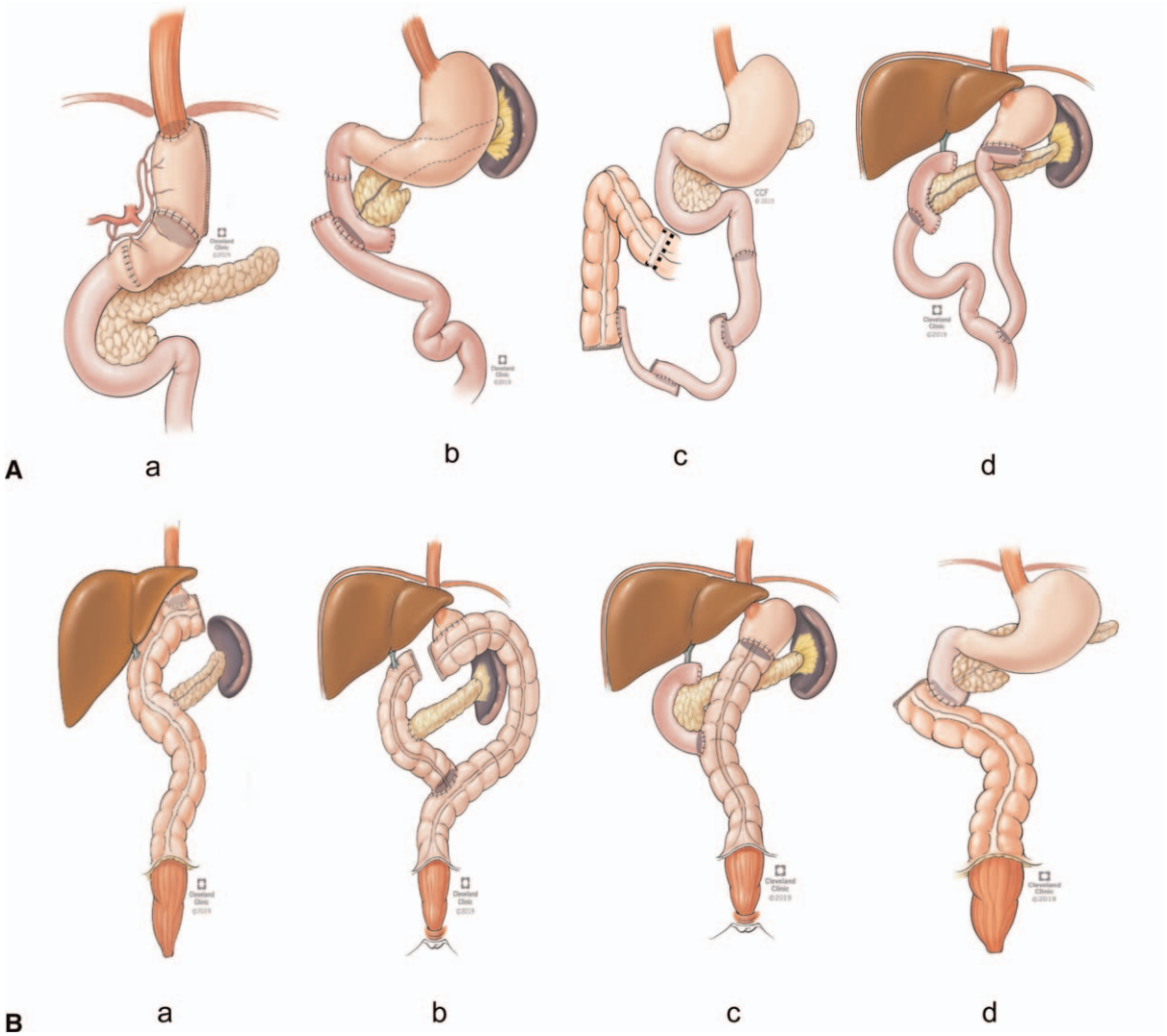

FIGURE 2. A, Primary autologous gut reconstruction (AGR). (a) Primary foregut reconstruction of including different combinations of esophagogastric and gastrogastric anastomoses with gastroplasty and pyloroplasty. Note preservation of the left gastric arterial branches. (b) Duodenal reconstruction with end-to-end anastomosis of D1 and side-to-side duodenojejunal anastomosis at D2 in a nonshort gut syndrome patient with complex duodenal fistula. (c) Multiple mid-gut and hindgut reconstructions with tailored end-to-end, end-to-side, and side-to-side anastomoses. (d) Roux-en Y gastrojejunal and jejunojejunal anastomoses after a Whipple operation retaining the previous pancreaticojejunal anastomosis. B, Autologous reconstruction in patients with massive gut loss. (a) Drainage of the abdominal esophagus, biliary system, and pancreatic duct with a simple colonic loop construction. (b) Roux-en Y colonic reconstruction of the abdominal esophagus and pancreaticobiliary system in a patient with a relatively long residual colon. (c) Simple colonic drainage of the stomach and pancreaticoduodenal sweep. (d) Drainage of D2 with a duodenocolonic anastomosis in patients with massive mid-gut loss including D4-D3. C, Supra-diaphragmatic colonic alimentary conduit between cervical esophagus and infra-diaphragmatic gut; (a) stomach, (b) residual antrum, (c) jejunum with end-to-side anastomosis, and (d) Roux-en Y Jejunocolonic anastomosis in a patient with short colonic conduit because of prior partial colectomy. Note the requirement for a free-forearm flap as a second-stage operation in 2 patients (c, d) due to poor perfusion of the proximal end of the colonic conduit. D, Infra-diaphragmatic alimentary conduits. (a) Colonic interposition autograft between abdominal esophagus and duodenum. (b) Patching of a major D1–D3 lateral wall defect in a Crohn's disease patient with an isolated segment of transverse colon. (c) Roux-en Y esophagojejunostomy with neo-stomach (insert) utilizing the J pouch technique. (d) Jejunal conduit between abdominal esophagus and retained antrum.

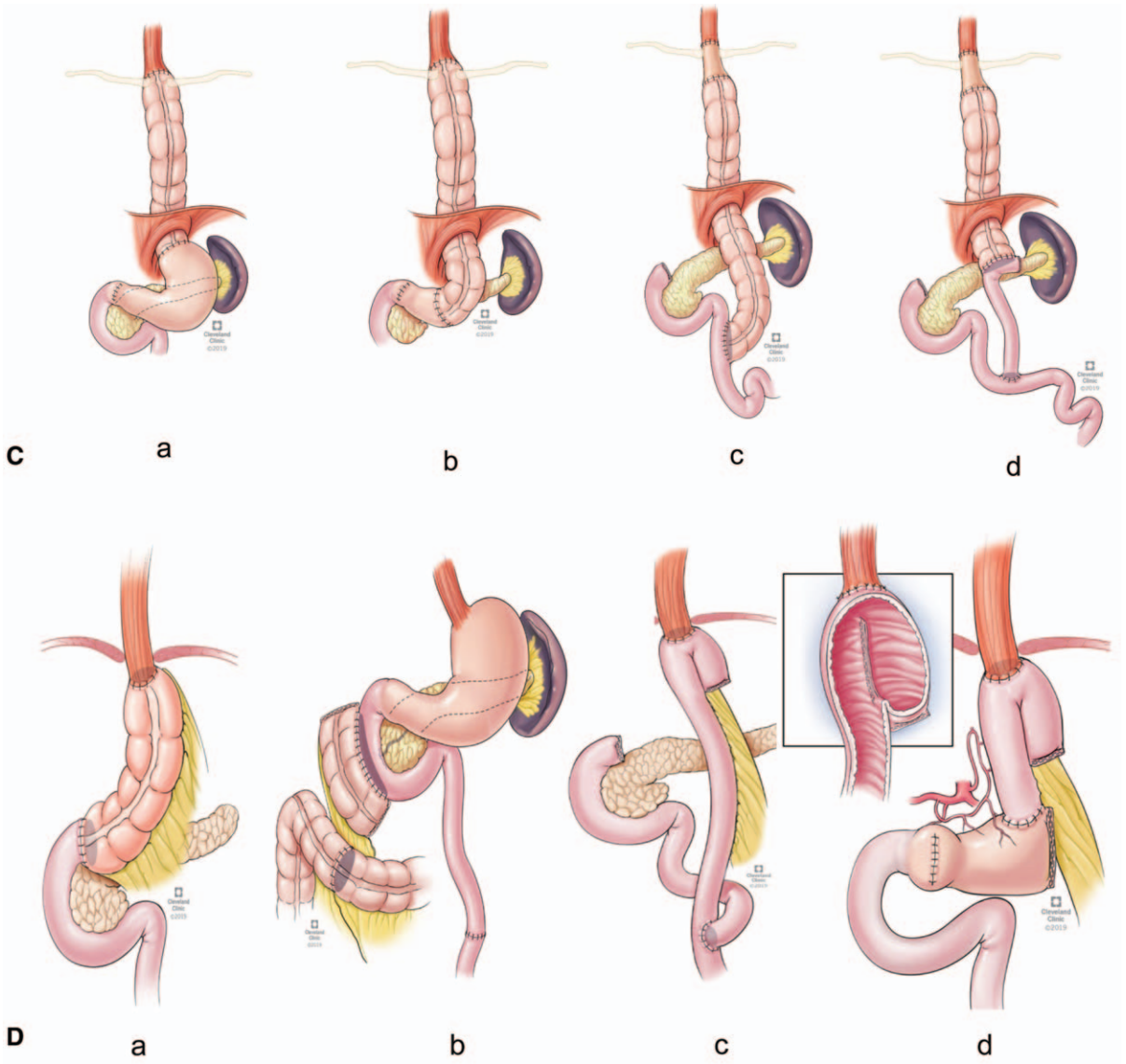

FIGURE 2. Continued

psychiatric disorders. Socioeconomic mile stones included education, marital status, and occupation.

Statistical Analysis

Data was pooled and stratified according to type of GF and treatment modality. The subsequent need for transplantation substratified AGR patients and transplant recipients were categorized according to type of allograft. Data was summarized as mean ± standard deviation or median [IQR] for continuous and percentage for categorical variables. Group differences were assessed with ANOVA, nonparametric Kruskal–Wallis rank-sum, and unpaired *t* test. Noncontinuous variables were examined using the Person chi-squared test.

Survival and restored nutritional autonomy (RNA) were calculated with the Kaplan–Meier product limit and cumulative event plot, respectively. Univariate and multivariate analyses were conducted using cox proportional hazard regression to identify total population survival risk factors. Predictors of RNA after AGR were analyzed for the 337 patients who survived AGR-alone (n = 308) or after cross-over to transplant (n = 29). Group comparison was performed using the log-rank test. All events were computed as of February 20, 2019 and analyzed using R. package (R studio, version 3.5.2, Boston, MA).

Predictive Modeling

The 420 AGR patients were computed to develop an RNA predictive model. The multivariate independent predictors were used utilizing the binary logistic regression and time factor was determined by the median interval (4.5 mo) to TPN discontinuation. Patients who discontinued TPN before the 6 month mark were classified as events and those who were still receiving therapy were recorded as nonevents.[36]

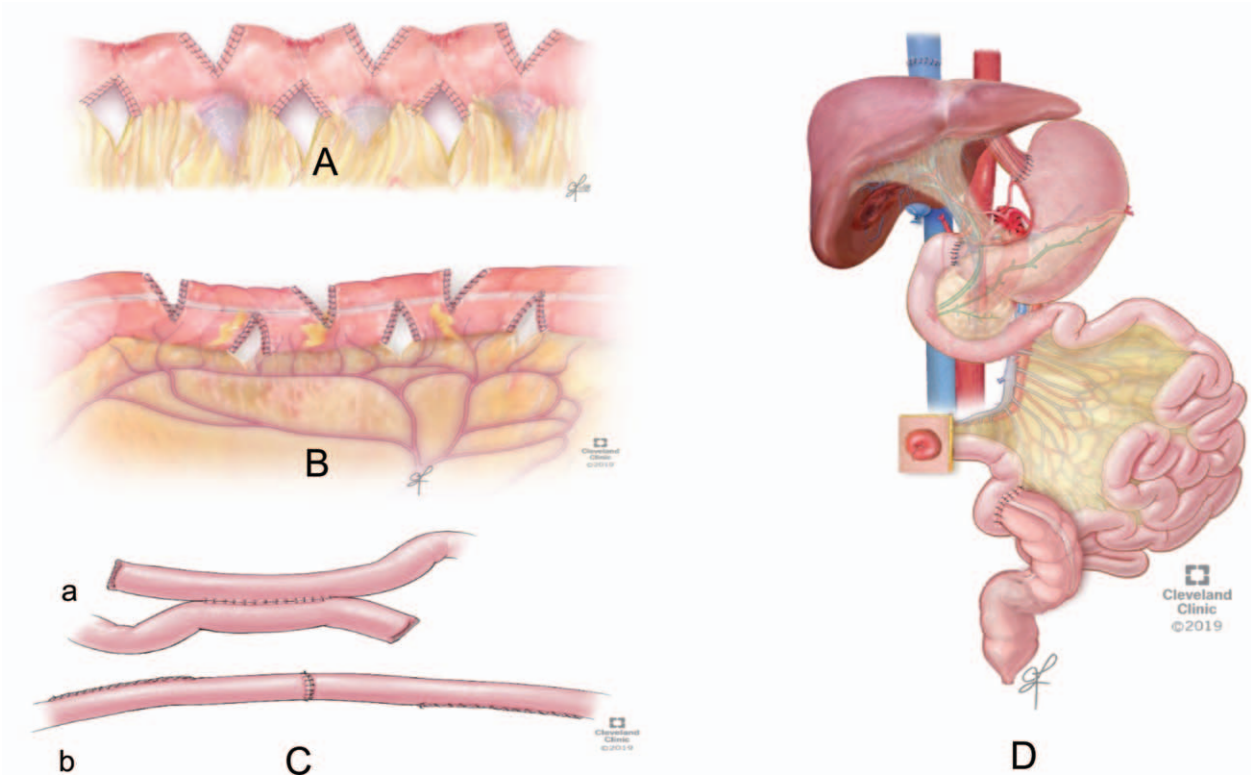

FIGURE 3. Surgical remodeling techniques. A, Serial transverse enteroplasty (STEP). Note over sewing of the staple lines and the scar tissue in between the cuts on the mesenteric border indicating a prior STEP procedure. B, The new technique of Serial transverse coloplasty (STCP) with preservation of the marginal arterial arcade of Drummond and avoidance of the watershed areas. C, Recruitment of healthy intestinal segments that are out of the alimentary flow in short gut syndrome patients with previous intestinal bypass surgery, blind pouches, and dilated side to side anastomoses (a). Note the bowel lengthening by longitudinal transection of the dilated anastomosis with reestablishment of an end-to-end reconstruction (b). D, The trifecta procedure with subtotal colectomy, pyloroplasty, and chimney ileostomy that is designed for patients with gut dysmotility.

The data was split into a training (n = 295, 70%) and test set (n = 125, 30%) with similar proportion of events and nonevents. Training set was used to develop the model and the bootstrap approach (100 bootstrapped samples) was used for validation. With multiple imputation of missing values, a conventional cut-off point of 0.5 was used classifying the probabilities into events (>0.5) and nonevents (≤ 0.5). Challenging the model was practiced using the test set. Model performance was examined using various metrics including area under the curve (AUC), accuracy, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

RESULTS

Descriptive Analysis

Total population expressed significant age, sex, ethnicity, and geographic disparities with higher ($P < 0.05$) percentage of surgical GF among minorities. The distinctive features of the 3 types of GF are documented in Table 1 and the AGR patient characteristics are given in Table 2. A high prevalence of Axis-I-II psychiatric disorders was observed particularity among those with neuromuscular GF. With SGS, there was a linear correlation between bowel length and plasma citrulline levels (Fig. 5).

With significant differences in age and sex, most of the liver-free recipients received pretreatment and the liver-contained recipients were jaundiced with higher incidences of splenectomy and portomesenteric venous thrombosis (Table 3). Surgical time, operative blood loss, and length of hospital stay were significantly higher with liver-contained transplant. With intestine-only transplant, estimated blood loss was 3.5 ± 3 units.

Surgical Complications

The Clavien–Dindo grade III-b AGR-associated complications were encountered in 56 (13%) patients with a total of 64 events (Table 4). These were anastomotic leak/bowel perforations (n = 21), postoperative bleeding (n = 14), infections (n = 13), thromboembolism (n = 6), segmental colonic conduit ischemia (n = 2), and late bowel obstruction (n = 8). Most of the bowel perforations were thermal injuries and 2 of the surgical leaks occurred at the STEP staple lines. Surgical and/or radiologic interventions were required with a second-stage fore-arm flap reconstruction in 2 of the colon-bypass patients (Fig. 2C). Treatment was life-saving in all but 7 (13%) patients.

Transplant Morbidities

A total of 19 major surgical complications were documented in 14 (17%) recipients. These were sepsis (n = 6), severe pancreatitis (n = 4), allograft venous thrombosis (n = 3), bleeding (n = 3), anastomotic gastric leak (n = 2), and ruptured infra-renal aortic graft (n = 1). All patients underwent prompt surgical intervention

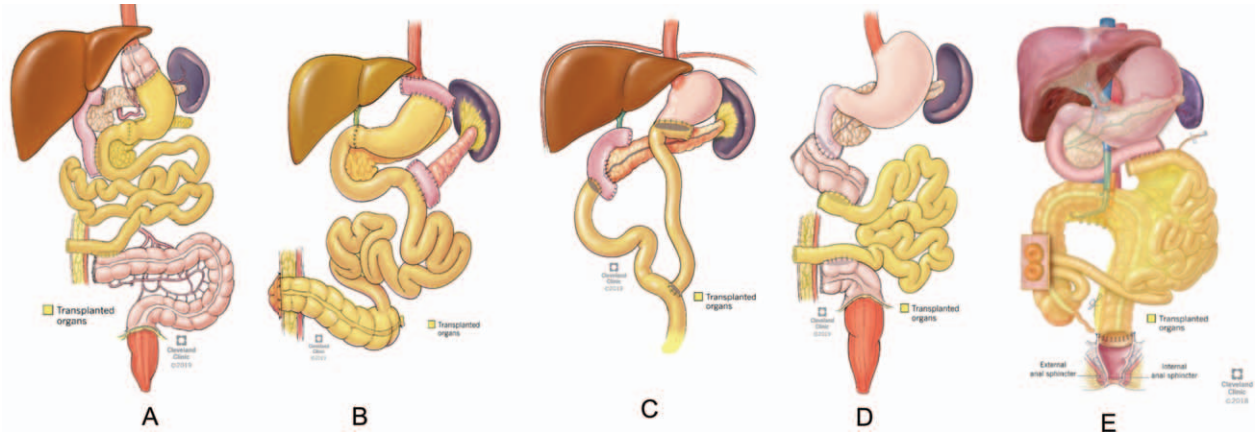

FIGURE 4. Various modifications of the recipient operation according to the previous AGR and required type of allograft. A, Preservation of pretransplant esophagocolonic anastomosis in a modified multivisceral recipient with part of the native colon being utilized as a conduit between short abdominal esophagus and transplanted stomach. Note preservation of the native duodenum, pancreas, and spleen. B, A full multivisceral recipient with prior total gastrectomy and Whipple procedure preserving the esophagojejunal and jejunopancreatic anastomoses with utilization of the two native jejunal segments as conduits between native and transplanted visceral organs. C, An isolated intestinal retransplant recipient with prior Whipple procedure employing the native jejunopancreatic sweep for an upper gut reconstruction with a Roux-en Y technique utilizing the allograft jejunum. With this technique, the native spleen and pancreas were preserved and the patient required intestine-only transplant. D, Preservation of previously reconstructed D2-duodenocolonic anastomosis in an isolated intestinal recipient. The previous AGR eliminated the need for a composite visceral allograft. E, A pull-through operation with en-bloc colonic allograft restoring continuity of hindgut in patients with preserved anal sphincters.

including enterectomy (n = 3) and total allograft pancreaticoduodenectomy (n = 1). Death was inevitable with the ruptured aortic graft and in 2 patients with severe native pancreatitis.

Acute rejection was diagnosed within the first 90 postoperative days in 47 (50%) allografts that was irreversible in 8 (12%) of the liver-free and 1 (5%) of the liver-contained allografts. Chronic rejection was documented in 6 (6%) allografts. GVHD was diagnosed in 4 (5%) liver-contained allograft recipients including 3 adult patients. Two of the adults had neoplastic syndromes and the third developed GVHD after liver-contained retransplant. The child had Tricho-hepato-enteric syndrome with incidental hepatocellular carcinoma. With respective T and CD_8 circulating donor cells of 53% and 74%, none of the patients responded to altered immunosuppression and all died of infection. Posttransplant lymphoproliferative disorder was diagnosed in 5 (6%) and CMV in 2 (2%) adult recipients with all but 1 being successfully treated with reduction of immunosuppression and targeted therapy.[32]

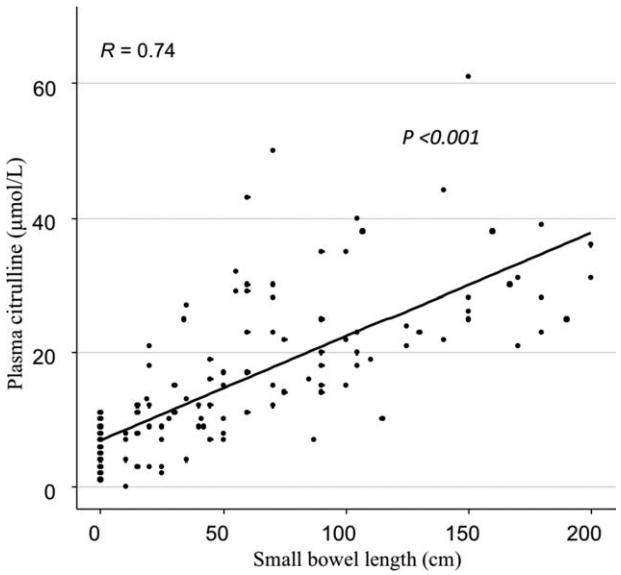

FIGURE 5. Linear correlation between levels of plasma citrulline and bowel length (cm).

Graft Loss and Retransplantation

Of the 94 allografts, 42 (45%) were lost because of patient death (n = 26, 62%) and allograft failure (n = 16, 38%) (Table 3). Nine underwent retransplantation including a child receiving a third transplant with an overall rate of 11%. The remaining 7 failed allografts were removed without retransplantation. Five died and 2 are awaiting retransplantation.

Survival

With a mean follow-up of 30 ± 23 months, 112 patients died with 22% mortality rate (Table 5). TPN-associated complications, malignancy, and surgical failure were the leading events after AGR with sepsis, allograft rejection, GVHD, and technical complications being the common causes after transplant. The 38 medically treated patients had a mortality rate of 32% with TPN-associated complications in 6 (50%). Of these, 2 died waiting for transplant. Other causes were cardiac (n = 4) and malignancy (n = 2).

With a total of 388 (78%) survivors, 308 were AGR, 54 were transplant, and 26 were nonsurgical patients. The overall cumulative survival was 86% at 1 year and 68% at 5 years (Fig. 6A). There was no significant difference comparing types of GF (Fig. 6B). Surgery including AGR and transplant achieved better (P = 0.05) survival

TABLE 5. Causes of Death Among the Autologous Gut Reconstruction and Gut Transplant Recipients

Autologous Gut Reconstruction		Gut Transplantation	
Cause	**No (%)**	**Cause**	**No (%)**
Surgical failure	7 (10)	Technical complications	3 (10)
Total parenteral nutrition-associated	19 (27)	Sepsis	10 (33)
Line-sepsis	14	Intra-abdominal gram negative	8
Liver failure	5	Fungal infection	2
Malignancy	15 (21)	Allograft rejection	6 (20)
Recurrence/progression	10	Acute	3
De-novo cancer	5	Chronic	3
Respiratory failure	6 (9)	GVHD	4 (13)
Cardiovascular	5 (7)	PTLD	2 (7)
Thromboembolic	4 (6)	End of life-care	2 (7)
Renal failure	4 (6)	Respiratory failure	1 (3)
End of life-care	3 (4)	Unknown	2 (7)
Suicide/drug over dose	2 (3)		
GVHD after stem cell transplant	1 (1)		
Anticoagulation therapy	1 (1)		
Unknown	3 (4)		
Total no.	70 (19)	Total no.	30 (36)

GVHD indicates graft verses host disease; PTLD, posttransplant lymphoproliferative disorders.

compared with TPN therapy with respective 5-year rates of 70% and 44% (Fig. 6C).

AGR-alone patients achieved 1 and 5-year survival rates of 88% and 74%. The survival benefit was similar among the 3 types of GF (Supplementary Figure-4, http://links.lww.com/SLA/B735). Primary transplant recipients experienced 81% cumulative survival at 1 year and 50% at 5 years with respective graft survival of 75% and 43% (Supplementary Figure-5, http://links.lww.com/SLA/B735).

Nutritional Autonomy

RNA was documented in 267 (69%) of the 388 total survivors; 219 (71%) AGR, 45 (83%) transplant, and 3 (8%) of the medically managed patients. In addition, 25 (22%) of the 112 total mortalities were free of TPN before death. The overall cumulative rate of RNA was 49% at 3 months, 63% at 1 year, and 78% at 5 years (Fig. 7A). Surgical treatment achieved significantly ($P < 0.0001$) better results with 5-year cumulative rates of 82% and 12%, respectively (Fig. 7B). Compared with AGR, transplant was more ($P = 0.03$) effective in restoring nutritional autonomy with 70% cumulative rate at 3 months and 85% at 5 years (Fig. 7C). With AGR, RNA was significantly ($P = 0.005$) higher with surgical compared with mucosal and neuromuscular GF (Fig. 7D). Interestingly, trifecta achieved a higher ($P = 0.8$) rate of RNA among the neuromuscular GF patients compared with a single or combined reductive/decompressive intervention with respective 71% and 55% rates at 3 years.

Both STEP/STCP and GLP-2 contributed to the reestablished nutritional autonomy. With a follow-up ranging from 4 to 72 months, bowel lengthening was associated with RNA in 44 (72%) of 61 survivors. Nine (56%) of the 16 GLP-2-treated survivors, 6 surgical and 3 medical, regained their nutritional autonomy within a median of 14 months. Of these, 5 (56%) were able to discontinue therapy with a sustainable effect for a median of 8 months.

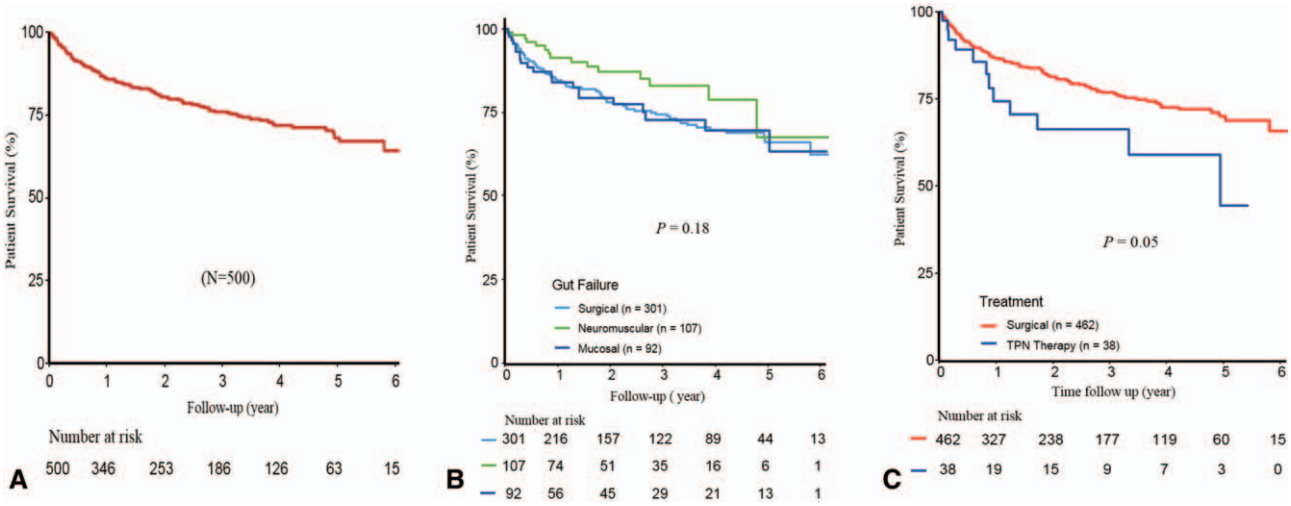

FIGURE 6. Kaplan–Meier cumulative patient survival: (A) Total population, (B) according to cause of gut failure, and (C) surgical versus total parenteral nutrition (TPN) treatment. Note the higher early survival with neuromuscular GF (B) and better long-term survival rate with surgical treatment (C). Note that the TPN patients are small cohort with high comorbidity index.

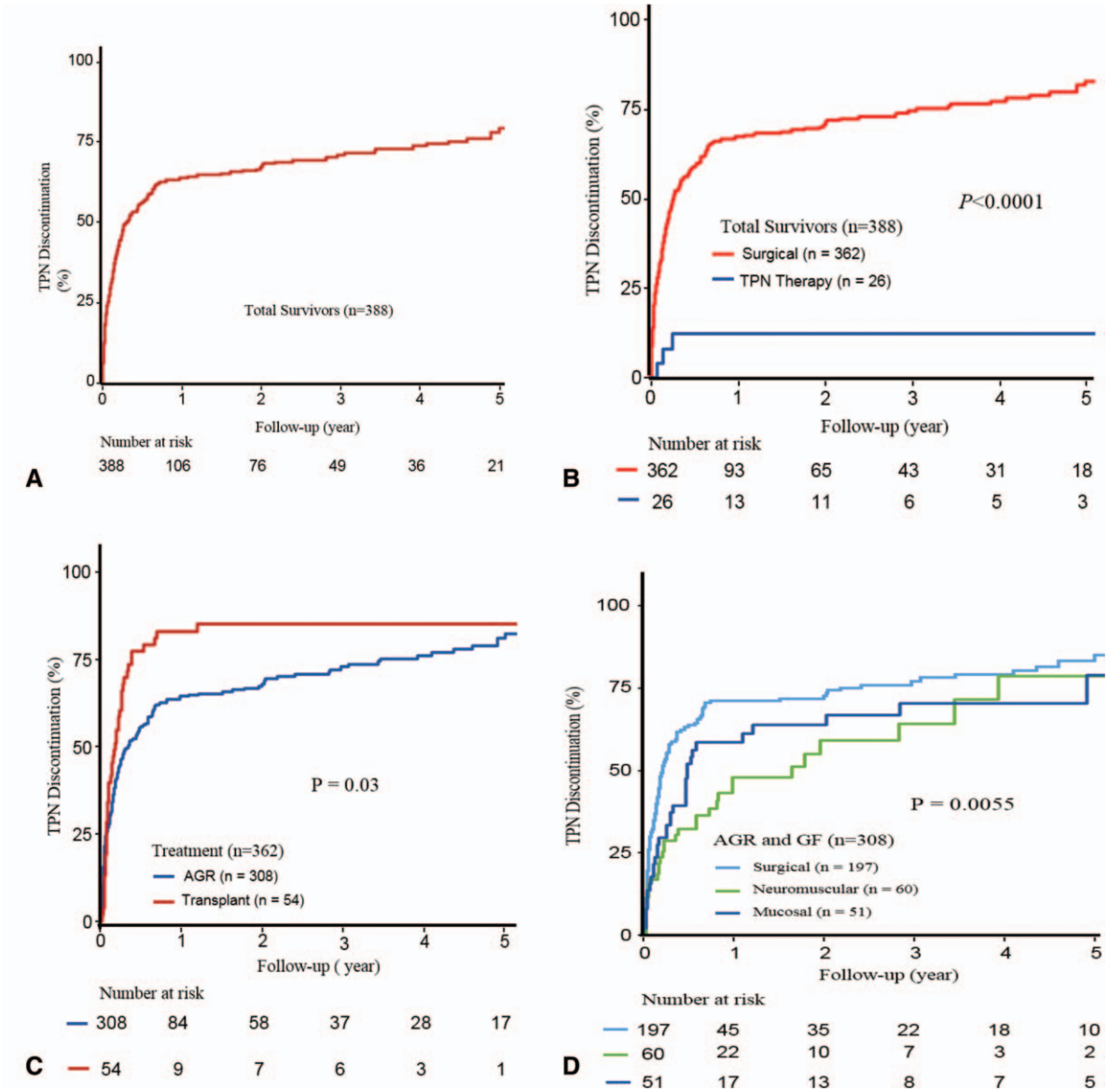

FIGURE 7. Cumulative achievement of nutritional autonomy with the establishment of a state of freedom from total parenteral nutrition (TPN). A, Total survivors. B, Surgical versus TPN therapy. C, Autologous gut reconstruction (AGR) versus transplant. D, According to cause of gut failure among AGR survivors. Note the significant therapeutic advantages of surgery particularly transplant and the better results among patients with surgical GF.

Most AGR and transplant TPN-free survivors had normal BMI with values ranging from 17 to 47 kg/m^2. Both serum albumin and prealbumin were within normal range with higher prealbumin values among transplant survivors. All vitamins, free iron, and zinc serum levels were normal with higher values after transplant (Table 6).

Disease Recurrence

Recurrence of nonmalignant disorders was observed in 23 (6%) of AGR and 6 (7%) of transplant patients with an overall incidence of 6%. The primary diseases of the AGR morbid cases were adhesions (n = 8), thrombophilia (n = 6), Crohn's disease (n = 5), radiation (n = 3), and mesenteric desmoids (n = 1). The transplant recipients had recurrent vascular thrombosis (n = 4), Crohn's disease (n = 1), and neuromuscular disorder (n = 1). With the exception of the 3 lost allografts due to venous thrombosis, all patients were successfully treated with targeted medical and surgical intervention.

Quality of Life

With an array of preoperative neuropsychiatric disorders, there were no significant changes after surgery (Table 7). The neurologic syndromes included a spectrum of posterior orthostatic tachycardia syndrome, autonomic dystonia, cerebral palsy, spina bifida, neurogenic bladder, and attention deficit hyperactivity disorder. The psychiatric disarrays included anxiety, depression,

TABLE 6. Current Nutritional Indices Among the Autologous Gut Reconstruction and Gut Transplant Survivors Who Achieved Full Nutritional Autonomy

	Autologous Gut Reconstruction	Gut Transplantation	*P*
No. of patients	219	45	
Age (mean ± SD, yr)	47 ± 16	36 ± 19	**0.001**
Body mass index (kg/m^2)	26 ± 7	26 ± 6	0.6
Serum albumin (range: 3.9–4.9 g/dL)	4 ± 0.4	4 ± 0.5	0.7
Serum prealbumin (range: 17–36 mg/dL)	22 ± 9	25 ± 11	0.2
Total 25-OH vitamin D (range: 31–80 ng/mL)	31 ± 15	47 ± 18	**0.001**
Vitamin A (range: 0.3–1.2 mg/L)	0.5 ± 0.2	0.7 ± 0.3	**0.001**
Vitamin E (range: 6–23 mg/dL)	10 ± 5	12 ± 5	**0.02**
Vitamin B6 (range: 20.125 nmol/L)	63 ± 58	73 ± 60	0.2
Vitamin B12 (range: 232–1245 pg/mL)	621 ± 429	928 ± 505	**0.006**
Free serum iron (range: 41–186 ug/mL)	68 ± 43	67 ± 44	0.8
Serum zinc (range: 55–150 ug/mL)	73 ± 20	75 ± 21	0.5
Follow-up (mean ± SD, mo)	26 ± 19	36 ± 18	**0.03**

TABLE 7. Quality of Life Measures Among the Autologous Gut Reconstruction and Gut Transplant Survivors Who Achieved Full Nutritional Autonomy

	Autologous Gut Reconstruction	Gut Transplantation	*P*
No. patients	219	45	
Children (current)	3 (1)	8 (18)	**<0.001**
Adults ≥ 65 yr old (current)	40 (18)	4 (9)	0.14
First-year readmission/patient	3 ± 2	6 ± 3	**0.001**
Gastrointestinal symptoms	219	45	0.399
Better	187 (85)	39 (87)	
Same	24 (11)	6 (13)	
Worse	8 (4)	0 (0)	
Oral medications (mean difference)	0.0 ± 5	14 ± 8	**0.001**
New onset chronic morbidities	219	45	
Hypertension	15 (7)	20 (44)	**<0.001**
Diabetes	10 (4)	10 (22)	**0.004**
Renal impairment*	5 (2)	13 (33)	**<0.001**
Renal failure	0 (0)	2 (4)	**0.002**
Major neurological disorders	30 (14)	1 (2)	**0.029**
Axis-I psychiatric disorders	111 (51)	27 (60)	0.245
Same/better	110 (99)	25 (93)	**0.037**
Worse	1 (1)	2 (7)†	
Socioeconomic status (adults)	216	37	
≥College education	104 (48)	34 (92)	**<0.001**
Marital status			0.197
Single	61 (28)	12 (32)	
Married	112 (52)	23 (62)	**<0.001**
Divorced	30 (14)	1 (3)	
Widow	13 (6)	1 (3)	
Occupation	216	37	
Employed	47 (22)	7 (19)	
Unemployed	19 (9)	2 (5)	
Retired	27 (13)	3 (8)	
Homemaker	8 (3)	13 (35)	
Student	8 (3)	1 (3)	
On disability	107 (50)	11 (30)	
Poor social support	30 (14)	1 (2)	0.08
Current Karnofsky/Lansky score	219	45	**0.005**
≥ 80%	163 (75)	29 (64)	
50%–79%	56 (25)	14 (31)	
<50%	0 (0)	2 (4)	
Follow-up (mean ± SD, mo)	38 ± 22	35 ± 18	0.42

*Serum creatinine ≥ 2 mg/dL.
†New onset cognitive disorder.

cognitive, somatoform, sleep, eating, substance related, and adjustment disorders.

It is reasonable to anticipate significant improvement in the socioeconomic milestones among the prereferral hospital-bound survivors. This study showed long-term stability in most of the socioeconomic landmarks including marital status and occupation with 5 of the AGR and 1 of the transplant patients giving birth or fathering a child (Table 7). However, there was a relatively large number of patients on disability in both groups with a higher ($P = 0.08$) prevalence among AGR (50%) compared with transplant (30%).

Of the 264 TPN-free surgical survivors, 192 (73%) resumed normal activities with no to minimal restrictions (Table 7). The remaining 72 (27%) patients, except 2 transplant recipients, were able to care for themselves with occasional requirement for assistance and mild more than moderate restrictive activities. Of these, 40 were senior citizens and 8 were children.

With higher Karnofsky/Lansky performance scores, AGR patients seem to have better QOL. The transplant recipients experience higher rates of recurrent hospital admission, new comorbidities, and daily need for numerous oral medications (Table 7).

Cost Analysis

With an average hospital stay of 19 days for 222 (59%) AGR and 40 days for 33 (39%) transplant patients, the total loaded cost per case was $69,382 for AGR and $297,010 for transplant. The average cost was $175,000 for liver-free and $325,000 for liver-contained transplant. The case mix index (CMI) was 1.04 to 5.46 with a mean of 3.25. Direct/indirect costs were $35,790/$33,592 for AGR and $197,453/$99,557 for transplant. In contrast, the reported yearly average charges were $250,000 for TPN and $300,000 for GLP-2.

Outcome Analysis

Predictors of survival and RNA, using univariate analysis, are summarized in Figure 8. With multivariate analysis, continuation of TPN, high comorbidity index, history of malignancy, prior thoracoabdominal transplants, thrombophilia, and advanced age were significant survival risk factors (Table 8). Anatomy of restored gut, duration and recipe of TPN, type of GF, and serum bilirubin were independent predictors of RNA among AGR survivors. These variables were carefully computed to build-up the RNA predictive model.

The RNA model was formulated with an accuracy of 75.6%, sensitivity of 75.5% and specificity of 75.7% (Supplementary Figure-6, http://links.lww.com/SLA/B735). The NPV and PPV were 72.5% and 78.4%, respectively. The AUC for the ROC was 0.84. For test data, accuracy was 74.4% and AUC was 0.815 with 85.1% sensitivity and 62.1% specificity. The NPV and PPV were 78.3% and 72.2%. These results support the validity of the model in predicting TPN discontinuation within 6 months after AGR. A software is provided for clinical application (website: http://projects.majestictech.co.in/rna/).

DISCUSSION

The intricacy of gut biology and energy homeostasis has delayed for many decades the management of GF. With better understanding of disease pathophysiology and recent advances in gut rehabilitation, efforts have been made to establish an integrated management approach.[18,23,24] Such a value-driven strategy has the

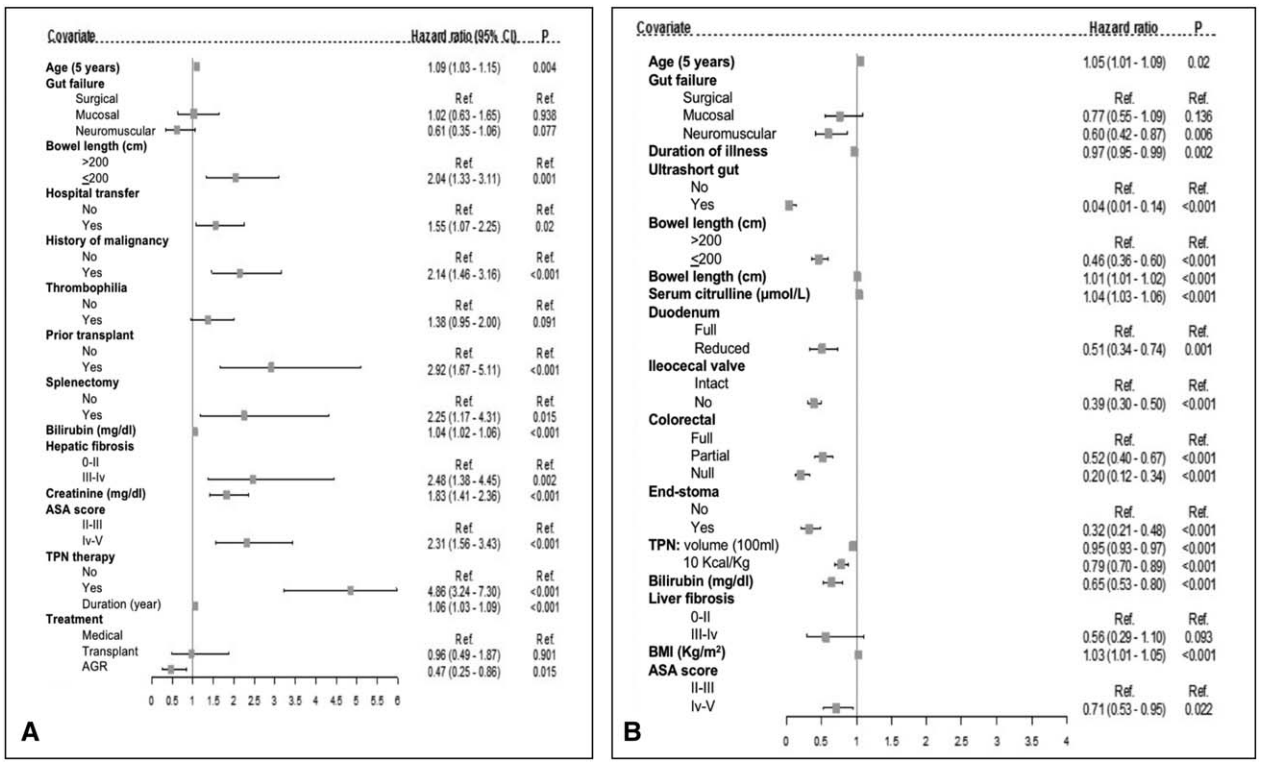

FIGURE 8. Foster plot of the univariate cox proportional hazard regression for the total population (n = 500) survival risk factors (A) and predictors of freedom from total parenteral nutrition (TPN) therapy (B) among the 337 autologous gut reconstruction survivors including 29 patients who ultimately underwent transplant and were censored as TPN dependent at that time. BMI indicates body mass index.

TABLE 8. Multivariate Survival Risk Factors and Predictors of Restored Nutritional Autonomy (RNA)

	Hazard Ratio	95% Confidence Interval	*P*
Total population survival risk factors (n = 500)			
Continuation of TPN therapy	4.95	3.26–7.51	**<0.001**
ASA comorbidity class (IV-V)	1.90	1.25–2.88	**0.003**
Prior nonintestinal thoracoabdominal transplant	1.90	1.06–3.42	**0.031**
History of abdominal malignancy	1.73	1.13–2.65	**0.011**
Thrombophilia	1.59	1.07–2.35	**0.022**
Age (5 yrs)*	1.11	1.04–1.18	**0.001**
Predictors of restored nutritional autonomy (RNA) among autologous gut reconstruction (AGR) survivors (n=337)			
Restored gut continuity without end stoma	1.49	0.95–2.31	0.080
Preoperative TPN duration (mo)	0.98	0.98 – 0.99	**<0.001**
Preoperative daily TPN volume (100 mL)*	0.96	0.94–0.99	**0.001**
Mucosal GF (surgical GF)*	0.96	0.66–1.40	0.845
Preoperative daily TPN calories (10 kcal/kg)*	0.84	0.74–0.95	**0.006**
Serum bilirubin (mg/dL)	0.75	0.60–0.93	**0.010**
Loss of ileocecal valve	0.67	0.50–0.89	**0.006**
Short gut syndrome ($\leq$ 200 cm)	0.67	0.49–0.92	**0.013**
Neuromuscular GF (surgical GF)*	0.32	0.22–0.48	**<0.001**
Ultra-short gut syndrome	0.07	0.02–0.29	**<0.001**

*Statistical reference.
ASA indicates American Society of Anesthesiologists; TPN, total parenteral nutrition; GF, gut failure.

potential to further advance the field with optimal utilization of native gut organs and judicious use of transplantation.[37,38]

This study is the first to systematically define the algorithmic management of GF patients utilizing an integrated surgical approach. Innovative autologous and transplant techniques were introduced with status of splanchnic organs, anatomy of residual gut, and cause of GF steering the ultimate care-path. These challenging organ-sparing and alimentary flow-restoring techniques were safe and effectively retrieved nutritional autonomy. Primary or adjunct use of bowel lengthening including the newly described STCP was effective in enhancing nutritional autonomy particularly in those with restored hindgut.[39–41] Remodeling of the gut in patients with neuromuscular insufficiency utilizing the introduced herein trifecta procedure may further advance the management of these severely disabling patients.[42,43] These complex open procedures are equally invaluable to the surgical residency training programs particularly in the current era of minimally invasive surgery.[44]

Gut transplantation should be reserved for patients who are not AGR candidates or fail weaning of TPN therapy. Despite the low probability of achieving nutritional autonomy in certain AGR patients, the procedure has the potential to rescue transplant candidacy, reduce the number of needed organs, and safely restore gut continuity. The current controversy concerning timing and listing criteria of transplantation should be revisited in the context of this study.[45–47]

Despite patient complexity and surgical challenges, the study population achieved excellent early survival with an acceptable 5-year attrition rate. The survival benefits were significantly better with surgical treatment compared with TPN therapy. However, it is important to note that the observed herein rate of TPN-associated mortality is higher than that reported in the SGS-TPN-dependent collective series.[5–7] This could be partially explained by the relatively small number of the TPN-study patients in the milieu of high morbidity index with coexisting malignancy and surgical contraindications.

Compared with transplant, AGR achieved better long-term survival. The higher attrition rate observed with transplant reflects the current use of the procedure as a rescue therapy compounded with the inherent risks of alloimmunity and long-term immunosuppression. The survival advantages of AGR were more evident among the mucosal and neuromuscular disease patients. The impact of gut pathology on survival with TPN therapy was also documented in a few collective review articles that focused on SGS patients with benign disorders.[5–7]

The achieved high rate of RNA is a testimony of the efficacy of the adopted integrated surgical management. Intrinsic gut disorders were associated with delayed onset and suppressed long-term RNA with no noticeable effect of disease recurrence. Such an interplay between primary gut disorders and RNA has also been reported among SGS patients.[5–7,48] More recently, 2 other single-center and consortium studies highlighted the significant role of gut anatomy and pathology on achieving enteral autonomy among children.[49,50]

With experience-based management policy, this study is the first to identify anatomy of reconstructed gut, severity of gastrointestinal insufficiency, type of GF, and serum bilirubin as independent predictors of RNA. The therapeutic efficacy of re-establishing gut continuity with normal alimentary flow emphasizes the complementary role of the different gut compartments in restoring energy homeostasis.[51–53] In addition to the loss of its physiologic function, absence of the ileocecal valve indicates a partially, or completely resected colon. Preoperative TPN duration, volume, and energy requirements are surrogate markers of severity of GF.[54] Type of GF and serum bilirubin reflects the in-depth chronic structural damage of the enterohepatic system. The interplay between these variables is the foundation of the described herein RNA model. It remains to be seen if plasma citrulline levels could reliably replace the anatomic and pathologic predictors in the model.[55]

The lack of QOL survey is a significant limitation in this study.[56–59] Alternatively, a combination of objective and subjective indicators was used. The highly prevalent axis-I psychiatric disorders may signal the crucial role of disrupted gut-brain-neuronal-circuits with altered neuropeptides and gut microbiota on human wellbeing.[60,61] Nonetheless, AGR survivors achieved higher performance than transplant recipients with fewer hospital readmissions, less comorbidities, and minimum oral medications. Unexpectedly, nearly half of the overall survivors were on disability. This could be partially explained by chronicity of the primary disease, old age, and fear of losing social security benefits.

The cost effectiveness of transplant was reported two decades ago with few recent publications.[62–65] However, this study is the first

to address the positive economic impact of integrated management with AGR being the most cost-effective modality. Further cost reduction is anticipated with early referral, efforts to reduce preoperative frailty, and establishment of a dedicated outpatient facility to reduce hospital stay and readmission. A new enterotrophic agent is also needed to replace the currently unaffordable GLP-2 treatment.

This study is the first to validate the concept of gut rehabilitation with evidence-based therapeutic advantages including survival, RNA, quality of life, and cost effectiveness. Until further progress in transplant tolerance, AGR should be honorably considered and transplantation judiciously utilized. Adjunct use of repeat bowel lengthening and enterocyte growth factor is useful for patients who continued to be TPN-dependent. Further progress is expected with growing experience utilizing the described herein novel surgical techniques and validated RNA predictive model.

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DISCUSSANTS

Dr Debra Sudan (Durham, NC):

Kareem, I wanted to congratulate you on this very large volume of experience in the treatment of patients with intestinal failure. As you know, these patients have few champions, and your leadership in this field has been evident for a long time. Your paper summarizes 750 referrals to the Cleveland Clinic, and of these, 500 comprised the study population.

In the manuscript, it appears that these are primarily those who underwent surgical management, either the AGR or transplant, and in a small number, both AGR and transplant. This leads to my first question.

Were the 250 that were not included not on TPN or did not require surgery? Or how did they differ from the 38 that were included in the study but that were treated with TPN only?

My second question is that of the 500 included, can you more clearly define the decision criteria, algorithm, and timing to determine which treatment was selected? Likewise, mixing of short bowel syndrome patients and other etiologies, for example, dysmotility is somewhat confusing because the goals for therapy and procedures would be expected to differ. So along the lines of your algorithm or treatment selection, how often was restoration of bowel continuity the goal of therapy versus improved function of a short remnant versus decrease in symptoms such as skin irritation from a complex enteroctuaneous fistula or bloating and pain in the a patient with dysmotility.

This is a comment really and not a question. You have included in Table 2 the volume and calories of parenteral nutrition as mean values for those undergoing AGR. I would encourage you to characterize these patients by the degree of TPN dependence in the same form that Loris Pironi has described from the European multicenter study. This is one that way we can standardize the description of this complex population.

Finally, I wanted to commend you on the wonderful figures regarding the novel innovative surgical reconstructions you have performed. I believe it was included in 18 of the patients undergoing AGR, and really demonstrated quite novel ways to reconstruct the GI tract. These are fabulous figures. Although these were the minority of the reconstructions, they could clearly serve as a textbook for options for patients in how to reconstruct these most complex patients.

Thank you again for the invitation to discuss, and I really enjoyed reading your paper and look forward to a revised version with these questions addressed.

Dr Kareem M. Abu-Elmagd

Thank you, Deb, for your kind words and flattering compliments. Your questions and comments are truly a testimony of your well-known expertise in the field. I will try to answer most if not all of your questions and respond to your comments. The 250 patients that were not included in the study were those with complex congenital and acquired gut disorders that maintained their nutritional autonomy and did not require TPN therapy at the time of referral. A good number of these patients had congenital malrotation and continued to have chronic gastrointestinal symptoms despite a prior Ladd procedure. As of to date, 50 of these patients with type-A malrotation underwent successful surgical reconstruction with innovative techniques and hopefully the association will give me the opportunity to present the data next year. The 38 patients that were included in the study and did not undergo surgical intervention fulfilled the inclusion criteria of GF with TPN dependence. With the exception of 6 patients listed for transplant, surgery was not warranted due to prohibitive operative risk, poor transplant candidacy, insurance denial, and patient's wish not to undergo surgery at that time.

Your second question is an excellent one. Keep in mind that the aim of the study was to restore the lost gut nutritional autonomy with discontinuation of TPN. Alleviation of patient symptoms was a secondary rather than a primary goal. Therefore, the decision to operate was based solely upon the presence of GF in the absence of prohibitive operative risk. AGR was adopted from the outset for all patients with residual gut anatomy and physiology that warranted successful surgical and functional outcome. It was also utilized in selected cases to rescue transplant candidacy. Transplantation was indicated only for patients with massive gut loss, concomitant liver and gut failure, failed AGR, and complex abdominal pathology that was not amenable for reconstructive surgery. These criteria guided the decision-making process and overall management algorithm. The timing of intervention whether AGR or transplant was dictated by

patient stability, coexistence of life-threatening morbidities, associated correctable organ dysfunction, and other concomitant psychosocial barriers.

The concern in regard to mixing short bowel syndrome patients with other etiologies of GF is an interesting one. In contrast to most of the currently published series that we both are aware of, this study is the first to address the entire spectrum of GF including a new classification with a novel management strategy utilizing innovative surgical techniques. Guided by the underlying pathophysiology, GF was classified into 3 main categories that guided the overall treatment tactics. Patients with surgical and acquired mucosal GF underwent AGR to recruit residual gut and restore continuity with reestablishment of normal alimentary flow. On the contrary, patients with neuromuscular GF required reductive/decompressive surgery to restore the alimentary flow. Such a remodeling triad procedure included subtotal colectomy, pyloroplasty, and diverting chimney ileostomy. The rational is to reduce overall gut stagnation and intraluminal pressure, enhance transit time, and ameliorate the risk of bacterial overgrowth. The trifecta procedure is indeed a remodeling one that overcomes the impaired gut motility in the milieu of intact enterocyte functions.

Your final comment encouraging the utilization of the recently published ESPEN categorical clinical classification of intravenous supplementation instead of actual TPN volume and calorie mean values is another interesting one. I am certain that you are fully aware of the descriptive nature of the classification with sincere attempts to homogenize a much diversified patient population with a wide range of intravenous supplementation. With the original 16 categories of ESPEN intestinal failure classification, the international multicenter cross-sectional study data were very fragmented, despite the huge number of recruited patients, with loss of its clinical and statistical merits. Despite the simplicity of the new 8 categories, the classification has yet to be validated as a useful tool for clinical use, translational research, or as a universal outcome metric. Such a legitimate concern is further magnified by the expected statistical loss of accuracy and validity upon converting continuous variables into categorical particularly in the setting of multivariate analysis and predictive modeling.

Dr Andreas Tzakis (Cleveland, OH):

I want to thank Dr Abu-Elmagd for sharing his manuscript with me. I think this is a landmark paper for 2 reasons. It establishes the value of autologous gut reconstruction in the treatment of these patients. It's remarkable you were able to achieve this, which is survival, nutrition, quality of life, and cost savings in 75% of these patients. Transplantation of the intestine has revolutionized the treatment of short-gut syndrome, and still it was only used here in 17% of the cases.

I think this study will be very difficult to be corroborated in many other centers for the following reasons: It requires a lot of skill, it requires a lot of vision, it requires tenacity, which is very characteristic of the senior author of this paper.

I have the following questions:

The intestinal dysmotility is a progressive disease. You have a 3-year nutritional autonomy in 72% of the patients with a trifecta procedure. What do you think is the long-term outcome of this? Is this a destination treatment, or is this a bridge to transplantation with a long interval?

The abdominal closure has always been a problem in these patients. Would you comment on how you did the abdominal closure? I noticed that you did not use abdominal wall transplantation in any of these cases.

Thank you very much. I enjoyed reading the paper.

Dr Kareem M. Abu-Elmagd

Thank you very much, Dr Tzakis, for reviewing the manuscript. I agree with your generalized statement that gut dysmotility is a progressive disease with a natural history that has yet to be fully defined. This very disabling syndrome is caused by a wide variety of primary and secondary causes that may determine the pace of disease progression. The trifecta procedure was initially introduced as a bridge to transplantation particularly in patients with interim contraindications and those who, to begin with, had no interest in pursuing transplantation. With the observed continual improvement in oral tolerance in some of these patients, the operation was increasingly utilized with a cumulative increase in restoring nutritional autonomy as shown in the presentation. I agree with you Andy that some of these patients may once more lose their oral tolerance with an attrition rate that could be driven by the underlying pathobiology of each individual disease entity. It is my expectation that patients with genetic disorders may continue to deteriorate overtime requiring organ replacement.

We both know that abdominal wall closure has been a difficult task since we started together the journey of gut transplantation in Pittsburgh nearly 3 decades ago. Simple skin closure is our common practice particularly in patients with gut-atmospheric fistulae, infected surgical mesh, and contracted abdomen with the occasional need for temporary Alloderm graft. The technically inevitable ventral hernia can be easily repaired a few months later with component separation without the need for any synthetic or biologic material. The abdominal wall allotransplant obviously has no place among the AGR nonimmunosuppressed patients. All along, I have not been a fan of abdominal wall transplant because of the associated potential technical complications and expected long-term morbidities.

Dr Alan Livingstone (Miami, FL):

Just a comment. My disclosure is I don't do transplants but have watched with admiration the evolution of the intestinal transplant program we have at the University of Miami/Jackson Memorial Hospital. It started with Andy Tzakis and has now been expanded by Rodrigo Vianna to be perhaps the busiest in the USA, with 110 cases in the last 5 years. I noticed that over 50% of your patients are referrals (as are ours), and even more so than for liver transplants, I think intestinal transplants will end up concentrated in a few specialized referral centers. As a result of improved immunosuppression and newer techniques, the outcomes are vastly superior to a decade ago. In the last 2 and a half years, we have had survival of 100% of the children and 92% of transplanted adults with an excellent quality of life. I believe that the much improved outcomes, as exemplified by your results and other experienced centers, need to be more widely publicized so that more patients can be offered this life-changing procedure.

Dr Kareem M. Abu-Elmagd

Thank you, Dr Livingstone, for you comment. You are actually echoing what we stated and published nearly 20 years ago. However, my presentation today ushered in a new era with special emphasis on the evolving role of innovative autologous reconstructive techniques and other novel therapeutic modalities in the management GF without the need for transplantation. There is really nothing better than our own gut as clearly demonstrated in today's presentation with better long-term outcome including survival, quality of life, and cost effectiveness. However, gut transplantation came to stay but only for patients who are in actual need for it. Lastly, I want to quote what Josh Billing said more than a century ago ''I have finally kum to the koncluzion that a good reliable sett of bowels is wurth more tu a man than enny quantity ov brains.''

Dr Thomas Inge (Aurora, CO):

I'm impressed with the translation of the STEP procedure downstream to the colon, stepping on the colon, if you will. I'm wondering, though, from a biological standpoint—and I understand that your purpose in this is to slow transit time and improve absorption of water—but I'm wondering, if I'm a colonocyte and I'm feeling a threat to my life from this condition of short gut syndrome, I'm wondering if I'm turning on some of my genes that are there to absorb calories too. Are you seeing any caloric absorption from the colon that you STEPped? Because this could be quite an interesting biological phenomena if that is seen when the colon is used for the STEP.

Dr Kareem M. Abu-Elmagd

Oh, absolutely. We've done 12 patients. The first few, I was a little bit nervous to see if the colon was going to get ischemic. This did not happen since we always preserved the marginal arterial circulation and avoided the cuts in the shaded areas. In addition to its wet-weight absorptive capacity, the colon plays a significant role in the natural adaptation process following massive intestinal resection by digesting and absorbing energy from carbohydrates and medium-chain triglycerides with upregulation of the colonic peptide transporter PepT1, also known as SLC15A1. With serial coloplasty, it is reasonable to believe that these different absorptive capacities are enhanced with increased chance of restoring nutritional autonomy. As a matter of fact, the number of bowel movements was reduced in some of these patients from more than 8 a day to 2 or 3. As you may well know Tom, It is impractical, in a clinical setting, to measure the colonic energy absorption.

Dr Jeffrey A. Norton (Stanford, CA):

This is a fantastic paper. In the patients with the foregut problems, did you compare the colon interposition to the jejunal interposition, and was the jejunal interposition supercharged?

Dr Kareem M. Abu-Elmagd

This is a small number of patients, Dr Norton, but your question is very valuable. We didn't do any functional studies. We utilized what was left from the gut, colon, or small bowel, with a vascular pedicle that allows utilization of the visceral conduit without any tension and with good alignment. So we were doing the different techniques based upon the availability rather than the preferential physiology of what's left from the gut. Thank you.