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ORIGINAL RESEARCH



## Gastrointestinal stromal tumor in North Africa and the middle east: updates in presentation and management from an 11-year retrospective cohort

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### ABSTRACT

**Objectives:** This study described the epidemiological, clinical, and survival profiles of patients with gastrointestinal stromal tumor (GIST) in North Africa and the Middle East (AfME).

**Methods:** This regional, multicenter, observational, retrospective study collected 11-year data on demographics, medical history, disease characteristics, current treatment approaches of GIST, the safety of the most common tyrosine kinase inhibitors (TKIs), second cancers, and survival status.

**Results:** Data of 201 eligible patients were analyzed: mean age was  $56.9 \pm 12.6$  years; 111 (55.2%) patients were men, 21 (10.4%) patients had previous personal malignancy. The most common clinical presentation of GIST was dysphagia [92 (45.8%) patients]. The stomach was the most common primary site in 120 (60.7%) patients, 171 (85.1%) patients had localized disease at diagnosis. 198 (98.5%) GIST cases were CD117/CD34-positive. Imatinib was used in the neoadjuvant (18/21 patients), adjuvant (85/89 patients), and first-line metastatic treatment (28/33 patients) settings. The most common non-hematological toxicity associated with TKIs was vomiting in 32/85 (37.6%) patients. Overall, 100 (49.8%) patients (95%CI: 42.8–56.7%) were alive and disease-free while 30 (14.9%) patients were alive with active disease.

**Conclusion:** Presentation of GIST in our AfME population is consistent with global reports, being more frequent in patients >50 years old and having the stomach as the most common primary site. Unlike what is usually reported, though, we did have more patients with lymphatic spread of the disease. Despite the global trend and advances in the treatment of GIST according to molecular profile, this is still far to happen in our population given the lack of access to molecular profiles and the high associated cost.

### ARTICLE HISTORY

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### KEYWORDS

Diagnosis; epidemiology; gastrointestinal stromal tumor (GIST); markers; mutational analyses; tyrosine kinase inhibitors

## 1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract and are thought to arise from the same lineage as the interstitial cells of Cajal, a population of cells thought to be related to GI peristalsis and pacemaker activity. It comprises 0.1–3% of all gastrointestinal malignancies and affects 1.1 in every 100'000 people worldwide, but reliable epidemiological data are still limited [1–3].

In 2016, Soreide et al. published a systematic literature review of all available population-based studies on GIST, published between January 2000 and December 2014, and reported 29 studies comprising 13,550 patients from 19 different countries. From this analysis, the median age of diagnosis was in the 60-age group, with an equal gender distribution across most studies. While it can occur throughout the entire

GI tract, the stomach is the most frequent primary site of GIST, comprising 60% of all cases. Other primary sites reported are the small intestine (30%) and, less commonly, the rectum (3%), colon (1–2%), and esophagus (<1%). Extra-intestinal locations, such as the omentum, mesentery, and retroperitoneum were rarely reported [1].

Most GISTs are *KIT* or *PDGFR $\alpha$*  mutated (85%), while the other 10–15% are called wild-type. With further understanding of this disease, however, various other molecular subtypes were described and found to have different prognostic relevance and the treatment landscape of advanced and metastatic GIST involves identification of these and the use of targeted therapy [4]. The discovery of imatinib, a *KIT* tyrosine kinase inhibitor (TKI), in this disease, changed completely the treatment and outlook on it. Previously, surgery was the only viable option for these patients, as systemic chemotherapy has

always been largely ineffective [5]. Unfortunately, GISTs are known to develop new mutations and acquire resistance to imatinib, and an important clinical challenge in the treatment of these resistant tumors.

Fortunately, there has been an increasing number of research and publications, and we believe this is mainly due to the need to (1) investigate whether real variation in population risk leads to extreme differences in incidence, (2) demonstrate new mutations in the *c-KIT* gene, and (3) introduce new treatment options tailored based on the molecular analysis of the tumor [6].

Although GIST diagnosis and treatment have been extensively investigated in Western countries, data on the Middle Eastern population are lacking, with no information on outcomes, incidence, and prevalence rate, as well as treatment profiles. In this context, the purpose of this retrospective study was to describe the epidemiological, clinical, and survival profiles of GIST cases in various countries in North Africa and the Middle East (AfME) region.

## 2. Materials and methods

### 2.1. Study design

This was a regional, multicenter, retrospective, observational study. Data were retrospectively collected from medical charts and required collaborative work among medical oncologists, surgical oncologists, gastroenterologists, and pathologists involved in the management of GIST patients. Both public and private sectors were included, as well as both community and university centers. Patients diagnosed with GIST from January 2005 until December 2015 (11 years) in the AfME region were included.

### 2.2. Data collected

Data were collected by the provider and included demographics, medical history, disease characteristics upon diagnosis (clinical symptoms, physical and laboratory findings, positive diagnostic imaging modality, site of primary tumor and metastasis, and first diagnosis pathology), tumor features (mitotic activity, tumor size, complete resection, margins, surgery complications, and pathology characteristics), treatment with associated side effects, and survival status. The metastatic disease in lymph nodes was based on imaging and was histologically proved. The CTCAE was used to evaluate the safety events with TKIs.

### 2.3. Study endpoints

Since the study was epidemiological, no primary efficacy/effectiveness or safety endpoints were defined. Clinical outcomes were complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD), and were defined based on the response evaluation criteria in solid tumors (RECIST 1.1).

### 2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS for Windows Release (Version 24, IBM Corp, NY, U.S.A.) and STATA/SE 12.1 for Windows (STATA Corp. 2012, College Station, TX, U.S.A.). Data were summarized using descriptive statistics. Mean with standard deviation, or median and quartiles were reported for quantitative variables; and frequency distribution was used for categorical variables. When the date of birth was not recorded, the age at diagnosis was considered instead in the analysis. Survival analysis was done according to the Kaplan–Meier method and the log-rank test was used to compare survival between groups. Overall survival was calculated from the date of diagnosis to the date of death or date of the last follow-up, with 95% confidence intervals (CIs). Survival curves were generated using STATA/SE 12.1 for Windows. STATA Corp. 2012, College Station, TX, U.S.A..

### 2.5. Ethical considerations

Data were collected and analyzed in a confidential and anonymous way. This study was approved by the institutional review boards/independent ethics committees (IRB/IEC) of the participating sites (Table 1). It also followed the principles of the Declaration of Helsinki. Because of the retrospective nature of the study, a documented waiver for the informed consent document was used, as required by local regulatory authorities and/or IRB/IEC. The study was conducted in compliance with the Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

## 3. Results

### 3.1. Demographic characteristics and medical history

A total of 201 patients from six sites in four countries were included in the database. The mean age at diagnosis was  $56.9 \pm 12.6$  years old (range 22.7–93.4), with a male predominance (55.2%). The largest number of patients were from Lebanon (35.8%, 3 different sites), followed by Egypt (35.3%, 1 site), the Kingdom of Saudi Arabia (15.4%, 1 site), and Qatar (13.5%, 1 site).

Among the entire cohort of patients, 46.3% of the patients had medical conditions other than the GIST and the most reported one was hypertension (28.9%) followed by diabetes (17.9%). 21 out of the 201 patients (10.4%) had a history of another malignancy and 12 (6%) had a history of first-degree family malignancy (Table 2).

### 3.2. Disease and tumor characteristics

GIST was mainly diagnosed by a surgeon in our cohort, comprising of 40.8% of the patients, followed by gastroenterologists, in 25.4% of the patients. While 13.9% of the patients were asymptomatic at diagnosis, 45.8% presented with dysphagia, 13.9% had unexplained weight loss, 12.4% had abdominal pain or discomfort, and 11.4% with constipation/vomiting. Also, 33.3% of the patients had a palpable mass and

**Table 1.** Institutional review boards/independent ethics committees of the participating sites and local regulatory authorities.

Country	Institutional review boards/independent ethics committees (IRB/IEC) of the participating sites	Approval number/Date	Local regulatory authorities and/or IRB/IEC
Lebanon	IRB at Hammoud Hospital University Medical Center	V.1 of study protocol: approval issued on 29 November 2016 ( <b>no specific approval number</b> ) V.2 of study protocol: approval issued on 20 June 2017 ( <b>no specific approval number</b> )	IRB at Hammoud Hospital University Medical Center
	Ethics Committee at Hôtel-Dieu de France	V.1 of study protocol: approval issued on 30 November 2016 ( <b>File CEHDF 884</b> ) V.2 of study protocol: approval issued on 03 July 2017 ( <b>File CEHDF 884</b> )	Ethics Committee at Hôtel-Dieu de France
	IRB at the American University of Beirut	<b>SUR.ES.01</b> of 18 August 2017	IRB at the American University of Beirut
Saudi Arabia	IRB at King Fahad Medical City	<b>17-113</b> of 07 June 2017	Saudi Food and Drug Authority and IRB at King Fahad Medical City
Egypt	IRB at National Cancer Institute	V.1 of study protocol: <b>201617008.2</b> of 04 April 2017 V.2 of study protocol: <b>201617035.5</b> of 30 July 2017	Research Ethics Committee, Central Directorate for Research and Health Development, Ministry of Health and Population and IRB at National Cancer Institute
Qatar	Medical Research Center at Hamad Medical Corporation	<b>MRC-01-17-056</b> of 02 February 2018	Medical Research Center at Hamad Medical Corporation
Oman	Scientific Research Committee at National Oncology Center, Royal Hospital	<b>SRC#58/2017</b> of 01 August 2017	Scientific Research Committee at National Oncology Center, Royal Hospital

7% had abdominal distention at diagnosis (Table 2 and Table 3).

The stomach was the most common primary site in 60.7% of the patients, followed by the small intestine in 22.9% of patients, and the rectum in 4.5% of patients. The big majority of the patients (85.1%) had localized disease at diagnosis. For the 30 (14.9%) patients with metastatic disease, the most common sites for metastasis were the liver in 20 patients, followed by the lymph nodes (10 patients) and the peritoneum in 7 patients (Table 4). The metastatic disease in lymph nodes was closely located to the primary tumor.

Mean tumor size at diagnosis was  $9.6 \pm 6.7$  cm with 38.5% of the tumors described as bigger than 10 cm. Overall, 76/201 (37.8%) patients fell in the high-risk category and 58 (28.8%) patients fell in the low-risk category according to the Miettinen group classification. Among the pathology reports, 98.5% had reported CD117/CD34 positive. Other commonly reported IHC were: smooth muscle actin (41.3%), S-100 (30.8%), DOG1 (14.4%), desmin (11.9%), vimentin (10%), and cytokeratin (5%) patients. Only one patient (0.5%) had testing for oncogenic mutations with no available results. In total, 69.7% of the patients had complete resection of the tumor when first taken to surgery and 6.5% were diagnosed with perforated GIST (Table 5).

### 3.3. Treatment approaches

A total of 109 (54.2%) patients underwent laparotomy as a first surgical procedure to diagnose GIST while 27 (13.4%) patients underwent laparoscopy. A guided percutaneous biopsy or biopsy through endoscopy were done for 26 (12.9%) patients, each (Table 6).

#### 3.3.1. Primary localized GIST

Only 18 of the 201 patients (9%) received a neoadjuvant treatment with imatinib prior to the surgical procedure. The median time of duration of neoadjuvant therapy was 6 months. The main reason for discontinuing imatinib reported was the completion of planned treatment (38.9% of the patients). After neoadjuvant imatinib, one patient had a CR, while seven had a PR, two with SD, and one patient had a PD; unfortunately, data on the remaining patients were not available.

Overall, 85 (42%) patients of the total cohort received adjuvant therapy with TKI: imatinib being the primarily used in 95.3% of these patients, and sunitinib also being reported to be used in 1.2% of the patients. Among the patients who received adjuvant imatinib, 14.1% of patients had disease progression while on therapy and 15.8% developed progression after discontinuation of the imatinib, either local progression or metastatic disease.

#### 3.3.2. Metastatic GIST

Among the patients with metastatic GIST, 90.3% received first-line imatinib for a median period of 11.5 months, 9.7% sunitinib, and 3.2% nilotinib. Reason for choosing TKI was not specified. In patients who received first-line imatinib, 50% eventually developed resistance and progressed despite this therapy.

Patients who progressed on imatinib were later changed to a second-line TKI and throughout the cohort, sunitinib was the only TKI reported to be used as a second-line therapy. Median time of treatment on sunitinib was 23 months, and in 22.2% of the patients this therapy had to be held due to associated side effects. Third line-therapy was described in four patients only with nilotinib and regorafenib being used here.

**Table 2.** Demographics and medical history of the patients, diagnosing physician, clinical symptoms, and physical findings upon diagnosis (N = 201).

Countries	Lebanon (n = 72, 35.8%)	Egypt (n = 71, 35.3%)	Saudi Arabia (n = 31, 15.4%)	Other Arab countries (n = 17, 8.5%)	Other countries (n = 10, 5.0%)	Overall N = 201
Age at diagnosis†						
Mean ± standard deviation	60.5 ± 14.3	54.6 ± 12.4	58.9 ± 10.7	57.4 ± 11.6	51.9 ± 8.9	56.9 ± 12.6
[Range]	[24.1, 84.3]	[22.7, 84.8]	[46.5, 93.4]	[38.4, 72.7]	[33.3, 65.5]	[22.7, 93.4]
Median	63.4	55.3	53.9	60.5	53.8	56
Year of diagnosis, n (%)						
Unknown	9 (12.5%)	0 (0%)	1 (3.2%)	3 (17.6%)	0 (0%)	13 (6.5%)
2005	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
2006	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
2007	4 (5.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2%)
2008	4 (5.6%)	0 (0%)	0 (0%)	1 (5.9%)	1 (10%)	6 (3%)
2009	3 (4.2%)	13 (18.3%)	1 (3.2%)	4 (23.5%)	2 (20%)	23 (11.4%)
2010	9 (12.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (4.5%)
2011	5 (6.9%)	0 (0%)	1 (3.2%)	1 (5.9%)	1 (10%)	8 (4%)
2012	8 (11.1%)	5 (7%)	3 (9.7%)	1 (5.9%)	1 (10%)	18 (9%)
2013	7 (9.7%)	14 (19.7%)	2 (6.5%)	0 (0%)	1 (10%)	24 (11.9%)
2014	7 (9.7%)	16 (22.5%)	2 (6.5%)	2 (11.8%)	2 (20%)	29 (14.4%)
2015	13 (18.1%)	23 (32.4%)	21 (67.7%)	5 (29.4%)	2 (20%)	64 (31.8%)
Gender, n (%)						
Male	47 (65.3%)	35 (49.3%)	11 (35.5%)	11 (64.7%)	11 (100%)	111 (55.2%)
Female	25 (34.7%)	36 (50.7%)	20 (64.5%)	6 (35.3%)	6 (60%)	90 (44.8%)
Type of comorbidity, n (%)						
Hypertension	24 (33.3%)	11 (15.5%)	7 (22.6%)	12 (70.6%)	4 (40%)	58 (28.9%)
Diabetes	11 (15.3%)	9 (12.7%)	9 (29%)	6 (35.3%)	1 (10%)	36 (17.9%)
Dyslipidemia	8 (11.1%)	0 (0%)	0 (0%)	3 (17.6%)	0 (0%)	11 (5.5%)
Hepatitis C	0 (0%)	6 (8.5%)	0 (0%)	0 (0%)	0 (0%)	6 (3.0%)
Atrial fibrillation	3 (4.2%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	4 (2.0%)
Ischemic heart disease	0 (0%)	3 (4.2%)	1 (3.2%)	0 (0%)	0 (0%)	4 (2.0%)
Coronary artery disease	2 (2.8%)	0 (0%)	0 (0%)	2 (11.8%)	0 (0%)	4 (2.0%)
Obesity	1 (1.4%)	0 (0%)	0 (0%)	3 (17.6%)	0 (0%)	4 (2.0%)
Other (Table 3)	15 (20.8%) <sup>€</sup>	7 (10%) <sup>€</sup>	3 (9.7%)	4 (23.5%) <sup>€</sup>	1 (10%)	30 (14.9%)
History of GI disease, n (%)						
No	46 (63.9%)	67 (94.4%)	30 (96.8%)	15 (88.2%)	10 (100%)	168 (83.6%)
Yes	18 (25.0%)	1 (1.4%)	1 (3.2%)	2 (11.8%)	0 (0%)	22 (10.9%)
Unknown	8 (11.1%)	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	11 (5.5%)
Previous personal malignancy, n (%)						
No	46 (63.9%)	67 (94.4%)	30 (96.8%)	15 (88.2%)	8 (80%)	166 (82.6%)
Yes	16 (22.2%)	1 (1.4%)	1 (3.2%)	1 (5.9%)	2 (20%)	21 (10.4%)
Unknown	10 (13.9%)	3 (4.2%)	0 (0%)	1 (5.9%)	0 (0%)	14 (7.0%)
Family malignancy history (first degree), n (%)						
No	43 (59.7%)	56 (78.9%)	31 (100%)	15 (88.2%)	10 (100%)	155 (77.1%)
Yes	10 (13.9%)	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	12 (6.0%)
Unknown	19 (26.4%)	13 (18.3%)	0 (0%)	2 (11.8%)	0 (0%)	34 (16.9%)
Type of family malignancy (n = 8 out of 12 above with multiple answers), n (%)						
Breast	4 <sup>‡</sup>	0	0	0	0	4
Liver and bile duct	2	1	0	0	0	3
Stomach	2 <sup>‡</sup>	1	0	0	0	3
Bone	1	0	0	0	0	1
Lung	1	0	0	0	0	1
Urinary bladder	0	1	0	0	0	1
Uterine cervix	1	0	0	0	0	1

(Continued)

Table 2. (Continued).

Variable	Lebanon		Egypt		Saudi Arabia		Other Arab countries		Other countries		Overall
	(n = 72, 35.8%)		(n = 71, 35.3%)		(n = 31, 15.4%)		(n = 17, 8.5%)		(n = 10, 5.0%)		
Surgeon	27 (37.5%)	19 (26.8%)	24 (77.4%)	9 (52.9%)	0 (0%)	3 (30%)	0 (0%)	0 (0%)	82 (40.8%)		
Gastroenterologist	33 (45.8%)	8 (11.3%)	6 (19.4%)	4 (23.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	51 (25.4%)		
Multidisciplinary team	1 (1.4%)	2 (2.8%)	0 (0%)	2 (11.8%)	0 (0%)	6 (60%)	0 (0%)	0 (0%)	11 (5.5%)		
Oncologist	7 (9.7%)	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (4.5%)		
Gynecologist or urologist	0 (0%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	2 (1.0%)		
Unknown	4 (5.6%)	40 (56.3%)	0 (0%)	2 (11.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	46 (22.9%)		
Clinical symptom, n (%)											
Asymptomatic	1 (1.4%)	4 (5.6%)	17 (54.8%)	2 (11.8%)	4 (12.9%)	0 (0%)	0 (0%)	0 (0%)	28 (13.9%)		
Dysphagia	37 (51.4%)	36 (50.7%)	9 (29%)	8 (47.1%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	92 (45.8%)		
Unexplained weight loss	10 (13.9%)	10 (14.1%)	1 (3.2%)	6 (35.3%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	28 (13.9%)		
Abdominal pain or discomfort	7 (9.7%)	14 (19.7%)	2 (6.5%)	2 (11.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	25 (12.4%)		
Constipation	14 (19.4%)	5 (7%)	0 (0%)	2 (11.8%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	23 (11.4%)		
Vomiting	9 (12.5%)	10 (14.1%)	0 (0%)	4 (23.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (11.4%)		
Gastrointestinal bleeding (upper/lower)	6 (8.3%)	7 (9.9%)	4 (12.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	18 (9%)		
Anorexia	10 (13.9%)	2 (2.8%)	0 (0%)	3 (17.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (7.5%)		
Fever	11 (15.3%)	1 (1.4%)	0 (0%)	2 (11.8%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	15 (7.5%)		
Headache	7 (9.7%)	3 (4.2%)	2 (6.5%)	2 (11.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (7%)		
Abdominal mass	5 (6.9%)	4 (5.6%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)	11 (5.5%)		
Melena	4 (5.6%)	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	8 (4.0%)		
Fatigue	3 (4.2%)	1 (1.4%)	0 (0%)	3 (17.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (3.5%)		
Dizziness	4 (5.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	5 (2.5%)		
Urinary retention	0 (0%)	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	4 (2.0%)		
Nausea	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	3 (1.5%)		
Pain – back pain	3 (4.2%)	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (2.5%)		
Ascites	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)		
Night sweats	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)		
Other <sup>†</sup>	4 (5.6%)	5 (7%)	1 (3.2%)	3 (17.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (6.5%)		
Other (undefined)	3 (4.2%)	4 (5.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (3.5%)		
Physical finding, n (%)											
Palpable abdominal mass	12 (16.7%)	19 (26.8%)	22 (71%)	7 (41.2%)	0 (0%)	7 (70%)	0 (0%)	0 (0%)	67 (33.3%)		
Abdominal distention	4 (5.6%)	5 (7%)	5 (16.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	14 (7.0%)		
Pallor	0 (0%)	0 (0%)	3 (9.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)		
Abdominal tenderness	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)		
Epigastric tenderness	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)		
Fever	1 (1.4%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)		
Other <sup>‡</sup>	2 (2.8%)	11 (15.5%)	1 (3.2%)	3 (17.6%)	1 (3.2%)	2 (20%)	0 (0%)	2 (20%)	19 (9.5%)		
No answer	49 (68.1%)	45 (63.4%)	4 (12.9%)	6 (35.3%)	0 (0%)	2 (20%)	0 (0%)	2 (20%)	106 (52.7%)		

<sup>†</sup> Age at diagnosis = date of diagnosis – date of birth. 38 (18.9%) patients were reported without age at diagnosis due to missing date of birth or date of diagnosis or age at diagnosis.

<sup>‡</sup> One patient reported two cases of breast cancer in the family and one patient reported two cases of stomach cancer in the family.

<sup>§</sup> Patients with multiple other comorbidities.

<sup>¶</sup> Anal mass, bloating, bloody diarrhea, diarrhea (2), changes in bowel habits, cough, decrease in appetite, flatulence, gastritis, increased abdominal girth, lower bleeding, dyspnea, palpitation, and hypotension).

<sup>‡</sup> Underweight, suprapubic tenderness, sub serosal lesion, submucosal lump at gastroesophageal junction, small sub serous lesion found during sleeve gastrectomy, rectal mass, right perirectal mass, mass at the anal verge, lower gastrointestinal bleeding, rectum and anal canal, hepatosplenomegaly, hepatomegaly, cachexia, bilateral LL edema, bilateral inguinal lymph nodes, and lower limb swelling and tenderness.

Abbreviations: GI, gastro-intestinal; GIST, gastrointestinal stromal tumor.

**Table 3.** Other comorbidities ( $n = 36$ ).

Other comorbidities	Count	%
Benign prostatic hyperplasia	3	1.5
Hypothyroidism	3	1.5
Anemia	2	1.0
Osteoporosis	2	1.0
Chronic obstructive pulmonary disease	2	1.0
Hyperlipidemia	2	1.0
Asthma	2	1.0
Abdominal aortic aneurysm	2	1.0
Deep vein thrombosis	1	0.5
Cardiac disease	1	0.5
Aortic valve replacement	1	0.5
Carotid stenosis	1	0.5
Left ventricle concentric hypertrophy	1	0.5
Peripheral vascular disease	1	0.5
Cerebrovascular disease	1	0.5
Chronic venous ulcer	1	0.5
Cardiomyopathy	1	0.5
Chronic kidney disease	1	0.5
Psoriasis	1	0.5
Chronic eczema	1	0.5
Sleep apnea	1	0.5
Gastroesophageal reflux disease	1	0.5
Thyrotoxicity	1	0.5
Hepatitis B	1	0.5
Hyperthyroidism	1	0.5
Total abdominal hysterectomy for fibroids	1	0.5
<b>Total</b>	<b>36</b>	<b>18</b>

### 3.4. Safety of the most common TKIs

The most common associated complication with the use of TKIs was a change in their blood counts. Abnormalities in red blood cell counts and Hb level was the most reported one, followed by abnormalities in white blood cell count and platelet counts. The most common non-hematological toxicities reports related to the TKIs were: vomiting, diarrhea, constipation, and erythrodyesthesia syndrome (Table 7).

### 3.5. Survival status

By the end of data collection, 100 (49.8%) patients (95%CI: 42.8–56.7%) were alive and disease-free, while 30 (14.9%)

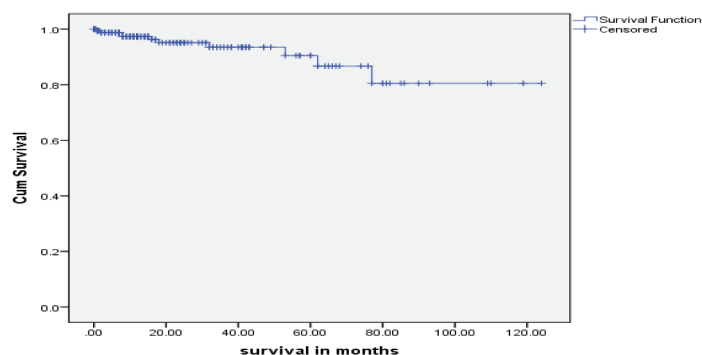
were alive with active disease. In parallel, 5% of the entire cohort had passed away and 61 (30.4%) patients were lost to follow-up and information on survival status could not be obtained. The mean survival time was 109.6 months (95%CI: 100.3–118.9). One-year survival was 99.4%, 5-year survival was 97.3%, and 10-year survival was 95.1% (Figure 1). Survival data by TKI adjuvant treatment are displayed in Table 8.

## 4. Discussion

This retrospective study described the epidemiological, clinical, and survival profiles of 201 GIST patients in Egypt, KSA, Lebanon, and Qatar over 11 years between January 2005 and December 2015.

Demographic data on age and gender distribution were in agreement with published studies from Lebanon [10], Jordan [11], Kuwait [6], Qatar [12], Saudi Arabia [13], and Turkey [14,15] with a mean age at diagnosis ranging from 55 to 62 years old and with a male predominance. The most frequent primary sites of diagnosis, in accordance with the published data, are the stomach (60.7%), followed by the small intestine (22.9%) [10]. The vast majority of patients (85.1%) had localized disease at diagnosis and these data were also aligned with those observed in a 15-year real-life study on 70 patients with confirmed GIST from a Lebanese hospital tumor registry (2000–2015) [10] and the other regional [6,11–14] and international studies [16,17].

In this study, 13.4% of the patients underwent laparoscopy surgery and >50% of the 201 patients had a median tumor size of 8.1 cm (4.2; 13.0) which, theoretically, would limit the use of this modality of surgery because of an increased risk of tumor capsule rupture [18]. Because of this danger, the National Comprehensive Cancer Network (NCCN) recommends using laparoscopy in GISTs < 5 cm in size [19]. Nonetheless, many published series have shown laparoscopic surgery is possible with good results in larger GISTs up to 20 cm in size [9,19–21], provided the surgeon can manipulate the large tumor without violating the capsule and can remove it through a laparoscopic incision [18].



**Figure 1.** Kaplan–Meier overall survival curve ( $N = 201$ ). Graph generated using STATA/SE 12.1 for Windows. STATA Corp. 2012, College Station, TX, U.S.A.

Table 4. Positive diagnosis imaging modality and site of primary tumor and metastasis (N=201).

Countries	Lebanon (n = 72, 35.8%)	Egypt (n = 71, 35.3%)	Saudi Arabia (n = 31, 15.4%)	Other Arab countries (n = 17, 8.5%)	Other countries (n = 10, 5.0%)	Overall N = 201
Positive diagnosis imaging modality, n (%)						
CT-scan	44 (61.1%)	62 (87.3%)	31 (100%)	12 (70.6%)	9 (90%)	158 (78.6%)
Ultrasoundography	6 (8.3%)	29 (40.8%)	0 (0%)	3 (17.6%)	4 (40%)	42 (20.9%)
PET-CT	10 (13.9%)	2 (2.8%)	0 (0%)	1 (5.9%)	1 (10%)	14 (7%)
Endoscopy	12 (16.7%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	13 (6.5%)
Gastroscopy/gastric endoscopy	4 (5.6%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	5 (2.5%)
Magnetic resonance imaging	5 (6.9%)	4 (5.6%)	0 (0%)	1 (5.9%)	2 (20%)	12 (6%)
Colonoscopy	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	2 (20%)	3 (1.5%)
Esophagogastroduodenoscopy	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
Guided biopsy	1 (1.4%)	0 (0%)	0 (0%)	1 (5.9%)	1 (10%)	3 (1.5%)
Other (plain abdominal X-ray, barium enema, surgery)	1 (1.4%) <sup>ε</sup>	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
No answer	15 (20.8%)	2 (2.8%)	0 (0%)	2 (11.8%)	0 (0%)	19 (9.5%)
Site of primary tumor, n (%)						
Stomach	42 (58.3%)	33 (46.5%)	28 (90.3%)	13 (76.5%)	6 (60%)	122 (60.7%)
Small intestine	16 (22.2%)	23 (32.4%)	0 (0%)	4 (23.5%)	2 (20%)	45 (22.4%)
Rectum	0 (0%)	6 (8.5%)	1 (3.2%)	0 (0%)	2 (20%)	9 (4.5%)
Soft tissue or skin	0 (0%)	4 (5.6%)	2 (6.5%)	0 (0%)	0 (0%)	6 (3.0%)
Colon	3 (4.2%)	2 (2.8%)	0 (0%)	0 (0%)	0 (0%)	5 (2.5%)
Mesentery	2 (2.8%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	3 (1.5%)
Pancreas/tail of pancreas	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Lymph nodes	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Duodenum (with small bowel)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Retropertitoneal	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Other/unknown <sup>t</sup>	0 (0%)	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
No data	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
Site of metastasis, n (%)						
Liver	6 (8.3%)	9 (12.7%)	3 (9.7%)	1 (5.9%)	1 (10%)	20 (10.0%)
Lymph nodes (based on imaging and histologically proved)	3 (4.2%)	5 (7%)	1 (3.2%)	1 (5.9%)	0 (0%)	10 (5.0%)
Peritoneum	1 (1.4%)	4 (5.6%)	0 (0%)	0 (0%)	2 (20%)	7 (3.5%)
Mesentery	2 (2.8%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
Lung	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
Small intestine	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Pleura	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Bone	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Spleen	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (0.5%)

<sup>ε</sup>One patient with two modalities.

Omental mass, multiple pelvi-abdominal masses, and one unknown.

Abbreviations: CT, computer tomography; PET-CT, positron emission tomography – computed tomography.

Table 5. Immunohistochemistry procedures and tumor characteristics (N = 201).

Variable	Lebanon		Egypt		Saudi Arabia		Other Arab countries		Other countries		Overall	
	(n = 72, 35.8%)	(n = 71, 35.3%)	(n = 31, 15.4%)	(n = 17, 8.5%)	(n = 10, 5.0%)	N = 201	Among those tested					
<b>Immunohistochemistry procedures, n (%)</b>												
C-KIT (CD117, CD34)	72 (100%)	71 (100%)	30 (96.8%)	15 (88.2%)	10 (100%)	198 (98.5%)	10 (100%)	4 (40%)	4 (40%)	198 (98.5%)	-	-
Smooth muscle actin	20 (27.8%)	42 (59.2%)	8 (25.8%)	9 (52.9%)	0 (0%)	83 (41.3%)	0 (0%)	2 (20%)	4 (40%)	83 (41.3%)	-	-
S-100	16 (22.2%)	43 (60.6%)	1 (3.2%)	2 (11.8%)	0 (0%)	62 (30.8%)	0 (0%)	2 (20%)	4 (40%)	62 (30.8%)	-	-
DOG1	5 (6.9%)	16 (22.5%)	0 (0%)	2 (11.8%)	0 (0%)	29 (14.4%)	0 (0%)	2 (20%)	6 (60%)	29 (14.4%)	-	-
Desmin	10 (13.9%)	7 (9.9%)	5 (16.1%)	2 (11.8%)	0 (0%)	24 (11.9%)	0 (0%)	2 (20%)	0 (0%)	24 (11.9%)	-	-
Vimentin	7 (9.7%)	5 (7%)	1 (3.2%)	6 (35.3%)	1 (10%)	20 (10.0%)	0 (0%)	1 (10%)	1 (10%)	20 (10.0%)	-	-
Cyokeratin	0 (0%)	10 (14.1%)	0 (0%)	0 (0%)	0 (0%)	10 (5.0%)	0 (0%)	0 (0%)	0 (0%)	10 (5.0%)	-	-
PDGFR	0 (0%)	1 (1.4%)	4 (12.9%)	0 (0%)	0 (0%)	5 (2.5%)	0 (0%)	0 (0%)	0 (0%)	5 (2.5%)	-	-
Caldesmon	2 (2.8%)	1 (1.4%)	0 (0%)	1 (5.9%)	0 (0%)	4 (2.0%)	0 (0%)	0 (0%)	0 (0%)	4 (2.0%)	-	-
Neuron-specific enolase	0 (0%)	0 (0%)	4 (12.9%)	0 (0%)	0 (0%)	4 (2.0%)	0 (0%)	0 (0%)	0 (0%)	4 (2.0%)	-	-
Epithelial membrane antigen	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)	-	-
Caietinin	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	-	-
Other†	3 (4.2%)	4 (5.6%)	1 (3.2%)	1 (5.9%)	0 (0%)	9 (4.5%)	0 (0%)	0 (0%)	0 (0%)	9 (4.5%)	-	-
<b>Mitotic activity, n (%)</b>												
<5/50 HPF	33 (45.8%)	27 (38%)	11 (35.5%)	11 (64.7%)	4 (40%)	86 (42.8%)	4 (40%)	2 (20%)	4 (40%)	86 (42.8%)	86/160 (53.8%)	-
>5/50 HPF	19 (26.4%)	32 (45.1%)	17 (54.8%)	2 (11.8%)	4 (40%)	74 (36.8%)	4 (40%)	2 (20%)	4 (40%)	74 (36.8%)	74/160 (46.3%)	-
Unknown	20 (27.8%)	12 (16.9%)	3 (9.7%)	4 (23.5%)	2 (20%)	41 (20.4%)	2 (20%)	0 (0%)	2 (20%)	41 (20.4%)	-	-
<b>Tumor size (cm)</b>												
Mean ± standard deviation	7.7 ± 5.9	12.1 ± 6.8	9.6 ± 7.6	8.7 ± 5.6	6.9 ± 5.4	9.6 ± 6.7	6.9 ± 5.4	3.3 (3.11)	3.3 (3.11)	9.6 ± 6.7	-	-
Median (Q1; Q3)	7 (3.5;10)	12 (7;15)	7.5 (3;14)	8.5 (4.7;12.5)	8 [0.5, 32]	8 [0.5, 32]	7.9 [1.8]	1 (10.0%)	1 (10.0%)	8 [0.5, 32]	-	-
IQR [Range]	6.5 [0.6, 33]	8 [0.5, 32]	11 [2.7]	7.9 [1.8]	5 (16.1%)	5 (16.1%)	1 (5.9%)	1 (10.0%)	1 (10.0%)	8.7 [0.5, 33]	-	-
Missing	7 (9.7%)	5 (7.0%)	5 (16.1%)	1 (5.9%)	0 (0%)	19 (9.5%)	0 (0%)	0 (0%)	0 (0%)	19 (9.5%)	-	-
<b>Tumor size (cm), n (%)</b>												
0 to ≤ 2	9 (13.8%)	2 (3%)	3 (11.5%)	3 (18.8%)	1 (11.1%)	18 (9.9%)	1 (11.1%)	0 (0%)	0 (0%)	18 (9.9%)	-	-
>2 to ≤ 5	13 (20%)	8 (12.1%)	8 (30.8%)	1 (6.3%)	4 (44.4%)	34 (18.7%)	4 (44.4%)	0 (0%)	0 (0%)	34 (18.7%)	-	-
>5 to ≤ 10	27 (41.5%)	19 (28.8%)	6 (23.1%)	7 (43.8%)	1 (11.1%)	60 (33%)	1 (11.1%)	0 (0%)	0 (0%)	60 (33%)	-	-
>10	16 (24.6%)	37 (56.1%)	9 (34.6%)	5 (31.3%)	3 (33.3%)	70 (38.5%)	3 (33.3%)	0 (0%)	0 (0%)	70 (38.5%)	-	-
<b>Miettinen risk classification, n (%)</b>												
High risk	-	-	-	-	-	76 (37.8%)	-	-	-	76 (37.8%)	-	-
Moderate risk	-	-	-	-	-	26 (12.9%)	-	-	-	26 (12.9%)	-	-
High to moderate risk	-	-	-	-	-	12 (5.9%)	-	-	-	12 (5.9%)	-	-
Low risk (including low, very low and no risk of relapse)	-	-	-	-	-	58 (28.8%)	-	-	-	58 (28.8%)	-	-
Low risk of relapse	-	-	-	-	-	34	-	-	-	34	-	-
Very low risk of relapse	-	-	-	-	-	16	-	-	-	16	-	-
No risk of relapse	-	-	-	-	-	8	-	-	-	8	-	-
Unknown risk because of missing data on mitotic index and/or size of the tumor	-	-	-	-	-	29 (26.4%)	-	-	-	29 (26.4%)	-	-
<b>Stomach</b>												
Small bowels	-	-	-	-	-	4	-	-	-	4	-	-
Other	-	-	-	-	-	7	-	-	-	7	-	-
<b>Complete resection, n (%)</b>												
Yes	51 (70.8%)	54 (76.1%)	24 (77.4%)	8 (47.1%)	3 (30%)	140 (69.7%)	3 (30%)	0 (0%)	3 (30%)	140 (69.7%)	140/174 (80.5%)	-
No	7 (9.7%)	14 (19.7%)	7 (22.6%)	4 (23.5%)	2 (20%)	34 (16.9%)	2 (20%)	0 (0%)	2 (20%)	34 (16.9%)	34/174 (19.5%)	-
Unknown	14 (19.4%)	3 (4.2%)	0 (0%)	5 (29.4%)	5 (50%)	27 (13.4%)	5 (50%)	0 (0%)	5 (50%)	27 (13.4%)	-	-
<b>Positive margins, n (%)</b>												
Yes	5 (6.9%)	17 (23.9%)	2 (6.5%)	0 (0%)	2 (20%)	26 (12.9%)	2 (20%)	0 (0%)	2 (20%)	26 (12.9%)	26/168 (15.5%)	-
No	51 (70.8%)	49 (69%)	29 (93.5%)	11 (64.7%)	2 (20%)	142 (70.6%)	2 (20%)	6 (60%)	2 (20%)	142 (70.6%)	142/168 (84.5%)	-
Unknown	16 (22.2%)	5 (7%)	0 (0%)	6 (35.3%)	6 (60%)	33 (16.4%)	6 (60%)	0 (0%)	6 (60%)	33 (16.4%)	-	-
<b>Perforation, n (%)</b>												
Yes	2 (2.8%)	1 (1.4%)	6 (19.4%)	2 (11.8%)	2 (20%)	13 (6.5%)	2 (20%)	0 (0%)	2 (20%)	13 (6.5%)	13/176 (7.4%)	-
No	57 (79.2%)	66 (93%)	25 (80.6%)	12 (70.6%)	3 (30%)	163 (81.1%)	3 (30%)	0 (0%)	3 (30%)	163 (81.1%)	163/176 (92.6%)	-

(Continued)

Table 5. (Continued).

Countries	Lebanon (n = 72, 35.8%)	Egypt (n = 71, 35.3%)	Saudi Arabia (n = 31, 15.4%)	Other Arab countries (n = 17, 8.5%)	Other countries (n = 10, 5.0%)	Overall Among those tested N = 201 25 (12.4%)
Variable	13 (18.1%)	4 (5.6%)	0 (0%)	3 (17.6%)	5 (50%)	
Unknown						
Testing for oncogenic mutations, n (%)						
Performed	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (0.5%)
Not performed	72 (100%)	71 (100%)	31 (100%)	16 (94.1%)	10 (100%)	200 (99.5%)

<sup>†</sup>Actin, AE1/AE3, AFP, AML, CD34, CD1a, CD68/30/21/23/1a/45Ro, CD99, LN5, myogenin, BCL2/CD44, LCA, LCA/ALK, Melan A/HMB45, CK5-6.

Abbreviations: HPF, high power field; IQR, interquartile range; Q, quartile.

One patient had no answer reported for immunohistochemistry and others have multiple ones.

Even though lymph node involvement in GIST is rare, ranging from reported 1.1% to 3.4% in the literature, lymph node spreading occurred in 10 (5%) of the 201 patients [8,22,23]. This overall rate of 5% is equivalent to 33.3% of the 30 patients who were metastatic at diagnosis in our 11-year study and is higher compared to the 14.3% defined in the other 15-year Lebanese study [10]. One possible hypothesis for this would be if our population had a higher rate of succinate dehydrogenase (SDH)-deficient GISTs, as these tumors have specific morphologic characteristics including multinodular gastric wall involvement and occasional lymph node metastases, but a thorough molecular analysis would be needed to shed the light on this event [24].

As for immunohistochemistry, 99% of the GIST cases were CD117/CD34-positive. These findings are consistent with the results of an observational study conducted in 27 cases of GIST, whereby the authors found positive immunoreactivity for CD117 in 100% of GIST cases, for CD34 in 89%, and for alpha-smooth muscle actin in 48% [25]. However, none of the GIST cases showed immunoreactivity for S-100 protein in the same study [25], while S-100 was detected in 62 (30.8%) patients in the present study. Importantly, in this series, 11.9% of the cases showed positivity for desmin staining. While desmin is rarely seen in GIST, literature has determined that a small proportion of GIST tumors can express this protein [25].

On another note, while current data and studies on GIST have been focused on molecular genetic profiling, only one patient among the entire cohort underwent genetic testing. This point raises concerns about the lack of access to this type of test that could be determinant on the decision of treatment, but this was probably the case because such test was not recommended systematically during the study period between 2005 and 2015. This point confirms the concerns raised in the Middle East by experienced oncologists in terms of lack of standardization of care and limited access to mutational analysis [26].

This study showed that 14.1% of the patients had disease progression while on adjuvant therapy. This percentage is quite high noting that data were data collected from different Arab countries where treatment adherence is poor, with limited access to medications, and little knowledge on GIST in the region during the study period. These patients were surgically resected with a R1/R2 margin and/or high-risk GIST (as per literature, patients on high risk receive adjuvant therapy). In terms of criteria for choosing neoadjuvant or adjuvant therapy for GIST patients in AfME region, pre-operative (neoadjuvant) imatinib is only considered if surgical morbidity could be reduced by downstaging the tumor preoperatively. Treatment duration is 6 months in such cases. In the adjuvant therapy setting, treatment duration is one year since the data of ACOSOG Z9001 trial were published, but changed to 3 years based on the findings of the SSGXVIII/AIO trial [27]. Also, 'Miettinen risk stratification system' is used to define the risk group of patients [7,24]. Indeed, Middle-Eastern physicians mainly follow international recommendations by NCCN (92%), American Society of Clinical Oncology (ASCO; 55%), European Society for Medical Oncology (ESMO; 55%), and national guidelines (40%) [28].

Table 6. Surgical procedures (N = 201).

Countries	Lebanon	Egypt	Saudi Arabia	Other Arab countries	Other countries	Overall
Variable	(n = 72, 35.8%)	(n = 71, 35.3%)	(n = 31, 15.4%)	(n = 17, 8.5%)	(n = 10, 5.0%)	N = 201 % within
First surgical procedure, n (%)						
Laparotomy	46 (63.9%)	31 (43.7%)	24 (77.4%)	6 (35.3%)	2 (20%)	109 (54.2%)
Laparoscopy	18 (25%)	2 (2.8%)	1 (3.2%)	5 (29.4%)	1 (10%)	27 (13.4%)
Guided biopsy	2 (2.8%)	21 (29.6%)	2 (6.5%)	0 (0%)	1 (10%)	26 (12.9%)
Endoscopy	2 (2.8%)	16 (22.5%)	6 (19.4%)	1 (5.9%)	1 (10%)	26 (12.9%)
Tumor/Bowel/Gastrointestinal stromal tumors SP resection	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	3 (30%)	4 (2.0%)
Gastroctomy (partial, sleeve)	0 (0%)	1 (1.4%)	0 (0%)	2 (11.8%)	0 (0%)	3 (1.5%)
Fine needle aspiration	0 (0%)	0 (0%)	1 (3.2%)	0 (0%)	0 (0%)	2 (1.0%)
Hartmann's procedure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (0.5%)
Other <sup>†</sup>	2 (2.8%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
Second surgical procedure, n (%)	2 (2.8%)	24 (33.8%)	0 (0%)	1 (5.9%)	1 (10%)	28 (13.9%)
Laparotomy	2 (2.8%)	19 (26.8%)	0 (0%)	0 (0%)	0 (0%)	20 (10.0%)
Endoscopy	0 (0%)	3 (4.2%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)
Laparoscopy	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (1.0%)
Hernia repair	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Right lateral paranal incision: excision of the mass with mucosal resection	0 (0%)	1 (1.4%)	0 (0%)	1 (5.9%)	0 (0%)	1 (0.5%)
Third surgical procedure, n (%)	0 (0%)	4 (5.6%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Laparotomy	0 (0%)	4 (5.6%)	0 (0%)	0 (0%)	1 (10%)	5 (2.5%)
						71.4
						10.7
						7.1
						3.6
						3.6
						3.6
						100

<sup>†</sup>Examination under biopsy and true-cut biopsy of a well-defined para rectal mass 2–3 cm from anal verge, enterorrhaphy for small bowel wedge resection and partial resection of two small bowel segments and enterectomy with primary anastomosis and radiofrequency ablation to resect one liver lesion.

Overall, data on the tumor characteristics and treatment toxicities in the adjuvant and neoadjuvant settings are also aligned with those of the American and Lebanese studies [10,17]. Nonetheless, the present study underlined the gaps and challenges in the treatment of GIST, particularly the lack of therapy and molecular analysis in the participating countries.

Furthermore, only 5 (2.5%) patients had second cancers in the present study while a review of the literature yielded 20% of patients with GIST who will have other malignancies [14]. Importantly, a thorough workup is required for patients who present with gastrointestinal symptoms, such as bleeding or pain, since more than one type of malignancy may be present. As such, biopsy should be done for all patients with new clinical or radiological masses and a history of GIST to exclude a non-GIST malignancy [17]. A diagnostic pitfall may also occur with lymphocytes within GISTs since these may either be neoplastic small lymphocytes or non-neoplastic tumor-infiltrating lymphocytes. For example, in the present study, one case of leukemia involved a GIST. In parallel, immunohistochemistry allows to the distinction between low-grade B-cell lymphomas involving a GIST and tumor-infiltrating lymphocytes, which are often common in GISTs [29–31].

As for the survival analysis, the results from the current 11-year study and the other Lebanese study are aligned [10]. In total, seven patients were dead at the end of this study because of the disease and three because of other or unknown reasons versus two patients who were reported dead in the 15-year Lebanese study [10]. Unfortunately, given the high number of countries included and the heterogeneous data collection, we could not collect survival data for proper analysis.

The present study has four limitations. The first limitation is the lack of molecular profiling. The second limitation is the presence of missing data probably because of the observational and retrospective nature of the study. Nonetheless, similar studies with fewer missing data provided comparable results. In parallel, in rising countries with increased interest in research, researchers are trying their best to report new information with the minimum possible of missing data to help with unmet needs in the region. A third limitation is that survival of patients with localized GIST and those with advanced GIST is provided as a single survival plot, which makes interpretation of the survival results challenging. However, this common curve aimed to give a general idea on the outcomes of GIST patients in AfME region. Finally, results of this study should be interpreted with an understanding of the limitation of potential biases associated with observational studies, including confounding. Confounding should be addressed in a set of multivariate analyses adjusting for potential predictors, such as age categories, location of GIST, mitotic activity, and treatments received. By contrast, the strength of this study is that it allowed the description of the epidemiological and survival data of GIST patients over 11 years in three major medical centers in Lebanon in the absence of an active National Cancer Registry in the country.

**Table 7.** Global non-hematological toxicities among patients who received TKIs (N = 85).

Global non-hematological toxicities	Count	%	Grade						Unknown
			1	2	3	4	5		
Vomiting	32	37.6	23	3	1	2		3	
Diarrhea	30	35.3	23	2	3	1		1	
Erythrocytopenia syndrome	26	30.6	17	5	1	3			
Constipation	13	15.3	11		1	1			
Periorbital edema	6	7.1	3					3	
Gastritis	6	7.1	3	1				2	
Muscle Cramps	5	5.9	2					3	
Headaches	4	4.7	3					1	
(Bilateral) Lower limb edema	3	3.5		1				2	
Abdominal pain	3	3.5	1					2	
Peripheral neuropathy	3	3.5		1				2	
Dyspnea	2	2.4				1		1	
Bone aches	2	2.4						2	
Skin rash	2	2.4				1		1	
Dry skin	2	2.4		1				1	
Edema	1	1.2			1				
High blood pressure	1	1.2					1		
Impotence	1	1.2						1	
Nausea	1	1.2						1	
Carpopedal spasm	1	1.2	1						
Dizziness	1	1.2	1						
Generalized itching	1	1.2						1	
Loss of appetite	1	1.2						1	
Hypothyroidism	1	1.2			1				
Pericardial effusion	1	1.2	1						

**Table 8.** Survival status by TKI adjuvant therapy (*N* = 201).

	TKI adjuvant therapy					
	Unknown		Imatinib		Sunitinib	
	Count	%	Count	%	Count	%
Alive with no evidence of disease (95% CI)	47	44.3% (34.9%, 53.8%)	51	63.0% (52.4%, 73.5%)	2	50.0% (6.8%, 93.2%)
Alive with active disease	17	16.0%	11	13.6%	2	50.0%
Lost to follow-up	36	34.0%	15	18.5%	0	0.0%
Dead from disease	4	3.8%	3	3.7%	0	0.0%
Dead from side effects	0	0.0%	0	0.0%	0	0.0%
Dead from unknown reasons	2	1.9%	1	1.2%	0	0.0%
Duration of survival (months)	Mean ± standard deviation	20.9 ± 26.4	31.7 ± 25.1	54.0 ± 38.4		
	Range	0; 124	2; 119	1; 93		
	Median (Q1; Q3)	10.0 (3.0; 28.5)	23.0 (7.0; 42.5)	61.0 (15.8; 85.3)		

Abbreviations: CI, confidence interval; Q, quartile; TKI, tyrosine kinase inhibitor.

## 5. Conclusion

GIST is a relatively new disease with underestimated importance of the treatment by health-care providers in the participating countries. In the AfME region, challenges are related to poor treatment adherence and access to medications. There is also the problem of sub-standard treatments in some low-income countries. This retrospective study highlighted the particularities of the GIST patients in the AfME region by addressing the diagnostic challenges both radiological and pathological, as well as the therapeutic limitations. To overcome these challenges, the key decision-makers in the health authorities, payers, and health-care professionals (surgeons, oncologists, and pathologists) should develop a cohesive and practical roadmap for better management of this rare tumor in the region. These include better access to treatment and increased access to international clinical studies wherein patients may benefit from novel therapies without additional costs.

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## Declaration of financial/other relationships

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## Author contributions

F Farhat: study conception and design, medical management of patients, laboratory assessments, data collection, data analysis, manuscript writing, and approval. M Hussein: medical management of patients, laboratory assessments, data collection, manuscript writing, and approval. E Sbaity: medical management of patients, laboratory assessments, data collection, manuscript writing, and approval. A Alsharm: medical management of patients, laboratory assessments, data collection, manuscript writing, and approval. K Rasul: medical management of patients, laboratory assessments, data collection, manuscript writing, and approval. S Khairallah: cytology, molecular pathology, data collection, manuscript writing, and approval. T Assi: data collection, data analysis, manuscript writing, and approval. N Allahyerdi: laboratory assessments, data collection, manuscript approval. A Othman: medical management of patients, laboratory assessments, data collection, manuscript writing, and approval. J Kattan: medical management of patients, laboratory assessments, data collection, data analysis, manuscript writing, and approval. All authors reviewed and approved the manuscript.

## Data availability statement

The data that support the findings of this study are available from the corresponding author, Fadi Farhat, upon reasonable request.

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