Cancer Epidemiology 40 (2016) 39–46

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies

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ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form 29 October 2015
Accepted 30 October 2015
Available online 24 November 2015

Keywords:
Epidemiology
GIST
Incidence
Risk category
Distribution
Registry

ABSTRACT

Background: Gastrointestinal stromal tumours (GISTs) are rare, yet the most common mesenchymal tumour within the digestive tract. Lack of diagnostic criteria and no specific code in the ICD system has prevented epidemiological evaluation except from overt malignant cases in the past. A global estimate of incidence and disease patterns has thus not been available.
Methods: A systematic literature search of all available population-based studies on GIST published between January 2000 and December 2014 were reviewed. Descriptive epidemiological data are presented.
Results: The search found 29 studies of more than 13,550 patients from 19 countries that reported sufficient data for regional or national population-based statistics. Age at diagnosis ranged from 10 to 100 years, with median age being mid 60s across most studies. Gender distribution was equal across studies. On average, 18% of patients had an incidental diagnosis (range from 5% to 40%). Anatomical location of primary tumour in 9747 GISTs demonstrated gastric location as the most frequent (55.6%) followed by small bowel (31.8%), colorectal (6.0%), other/various location (5.5%) and oesophagus (0.7%). Most studies reported incidence at 10–15 per million per year. Notably, lowest incidence was in China (Shanxi province) with 4.3 per million per year. Highest incidence rates were reported also from China (Hong Kong and Shanghai areas), and in Taiwan and Norway (Northern part), with up to 19–22 per million per year.
Conclusions: Epidemiology of GIST demonstrates some consistent features across geographical regions. Whether the reported extreme differences in incidence reflect real variation in population risk warrants further investigation.

Contents

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http://dx.doi.org/10.1016/j.canep.2015.10.031

1. Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal tract [1]. Malignant GISTs were once viewed as one of the most treatment-refractory tumours, with very few patients showing clinical response to conventional chemo- and/or radiation-therapy. Further, mesenchymal tumours were not properly recognized as specific entities before the emergence of proper diagnostic tools. The recognition of the interstitial cells of Cajal as the likely precursor cell and, identification of the mutations in c-KIT and platelet-derived growth factor receptor α (PDGRF-α) further led to increased understanding of the biology [2,3]. The break of the millennium saw the first reports on successful treatment with imatinib for metastatic GIST [4,5], which has now evolved into use for recurrent disease and, in adjuvant and neoadjuvant regimens [6–10], followed by new targeted drugs [11]. Thus, within the past decade, GISTs have emerged from being poorly defined, treatment-resistant tumours to a treatable tumour entity used as a cancer model for multidisciplinary, targeted therapy [12–14].

Although, KIT (CD117) immunohistochemistry is a reliable diagnostic tool in the diagnosis of GIST [15], the (few) cases of KIT-negative GISTs, GISTs showing unusual morphology as well as GISTs which progress during or after treatment with imatinib/sunitinib can be a challenge for pathologists and clinicians [16]. Further, until the recent awareness of the disease with ensuing consensus reports [17], no reliable coding or diagnostic practice has been used in various registries or pathology labs across the world. Thus, while reports on very large numbers of patients have revealed new knowledge in terms of treatment and behaviour of

Table 1
Epidemiology of GIST reported in population-based studies.

Author (Refs.)	Study population	Population	Years incl.	GISTs (n)	Incidence per mill	Male: female ratio	Age, median (range)
Nilsson et al. [26]	Sweden; Western	1.3–1.6 mill	1983–2000	288	14.5	1.0	69 (10–92)
Tryggvason et al. [27]	Iceland; National	300,000	1990–2003	57	11.0	1.5	66 (24–89)
Goettsch et al. [28]	Netherlands; National	16 mill	1995 + 1998–2003	1169	12.7	n.r.	n.r.
Kim et al. [29]	Republic of Korea	48.5 mill	2001–2002	747	7.7	1.0	56.3[a] (10–83)
Steigen and Eide [30]	Norway; Northern	n.r.	1974–2003	102	19.0	1.6	66 (32–93)
Chan et al. [31]	China, Hong Kong	300,000–350,000	1995–2003	47	16.8–19.6	1.2	66[a] (n.r.)
Tran et al. [23]	USA, SEER data		1992–2000	1458	6.8		
Perez et al. [32]	USA (SEER and Florida)	n.r.	1992–2002	n.r.	6.9	n.r.	n.r.
Rubió et al. [33]	Spain; Girona	553,661	1994–2001	46	10.9	1.0	63 (26–90)
Mucciarini et al. [34]	Italy; Modena	633,993	1991–2004	124	14.2	1.0	69 (30–90)
Tzen et al. [35]	Taiwan	n.r.			13.0		
Mazzola et al. [36]	Switzerland; Southern	n.r.	1995–2002		14.7		64
Ahmed et al. [37]	UK; Mid Trent	n.r.	1987–2003	185	13.2	0.9	64 (18–93)
Yan et al. [38]	Canada, Calgary	958,610	2000–2004	22	6.8	0.7	62[a] (n.r.)
Brabec et al. [39]	Czech Republic and Slovakia	15 mill	2000–2008	278	5.2	1.0	60
Cassier et al. [40]	France, Rhone-Alps region	5.96 mill	2005–2006	131	11.0	0.75	66 (34–91)
Monges et al. [41]	France; national	62.9 mill	2005	535	8.5–10	0.9	65[a](19–93)
Cho et al. [42]	Korea, nationwide		2003–2004	1227	16–22		
Hartley et al. [43]	Pretoria, South Africa	2.35 mill	2000–2009	54			
Sandvik et al. [44]	Norway, Southwestern	300,000	1980–2009	52	7.4 (5.4–9.4)	0.8	67
Giljaca et al. [45]	Croatia, western Adriatic region	250,000	1997–2007	31	12.4	0.8	Mean 61.9 ± 12.8 years, range 34–81
Mastrangelo et al. [46]	3 European regions: Veneto, Italy Rhone-Alps, France Aquitaine, France	13 mill	2007–2008 2005–2006 2007–2008	368	13.6	1.0	
Manrique et al. [47]	Lima, Perú	n.r.	2002–2010	103	n.r.	1.0	mean 64 yrs, range 30–88
Wang et al. [48]	Shanxi Province, China	35.9 mill	2011	153	4.3	1.2	59 (24–79) years
Minarik et al. [49]	Slovakia		2004–2011	278			
Rubio-Casadevall et al. [50]	Spain, northern region (Girona)		1994–2005	82	12.4	1.0	
Czech registry et al. [51]	Czech and Slovak republic, nationwide	15 mill	2006–2013	1107	9.2	1.1	62 yrs (38–79)
Chiang et al. [52]	Taiwan	23.4 mill	1998–2008	2986	11.3–19.7		
Lv et al. [53]	Shanghai, China	30.4 mill	2000–2010	1923	21.1	1.0	60.05 ± 12.98 years (range: 12–87 years)

SEER denotes "Surveillance, Epidemiology, and End Results".
n.r. denotes "not reported".; n.a. denotes "not applicable".
[a] Reported as mean age.

the disease [18–21], the epidemiology from population-based perspectives is less well described. This is due to many reasons but most importantly the larger series may be biased in referral pattern in terms of diagnosis or treatment of those patients with a malignant potential, overt or metastatic disease [21–23], which may not reflect the true population-based incidence of all GISTs [24].

Thus, we performed a systematic review to assess the reported incidence, tumour location, and clinicopathological data in truly population-based studies.

2. Materials and methods

2.1. Literature search

A systematic search of the PubMed/Medline English literature from January 2000 until December 31st, 2014 was performed using the search terms "gastrointestinal stromal tumour", "GIST", "epidemiology", "incidence", "population-based". Case reports, or reports of less than 20 cases, were excluded. Excluded were also studies not describing the primary catchment population or region from which the patients derived, or, if this information could not be obtained by contacting the authors of identified articles. References in the identified articles were searched to identify further possible studies.

For any region(s) described and defined in a study, but for which the actual population numbers were not given, the population statistics denominator was obtained from population statistics given by the World Bank population data [25].

The literature was searched for reports published after year 2000 only to ensure best possible homogenous comparison in diagnosis and recognition of GIST. Studies relying on histopathology alone (without immunohistochemistry) were excluded. Studies confirming immunohistochemistry results with or without mutational analysis were included, but mutational analysis was not required per se for inclusion. For studies reporting several papers on the same population, the paper with reported population-based data on incidence, tumour location and patient characteristics was included.

2.2. Statistical analysis

Attempt at formal metaanalysis was not done due to the perceived heterogeneity in the identified studies. Descriptive data are presented collectively for those categories were information could be obtained.

3. Results

The search found 29 studies [23,26–53] from 19 countries that reported sufficient data for regional or national population-based statistics. The identified studies are given in Table 1.

3.1. Incidence and demographic data

The reported incidence shows some variation between the studies, with studies from Northern-Norway [30], China (Hong Kong [31] and Shanghai [53]), and Korea [42] reporting incidences as high as 19–22 cases per million inhabitants, which represents the upper range limit reported in the world literature. On the other hand, data from the Shanxi province in China [48], the Czeck republic and Slovakia [39], and North America (Canada [38] and

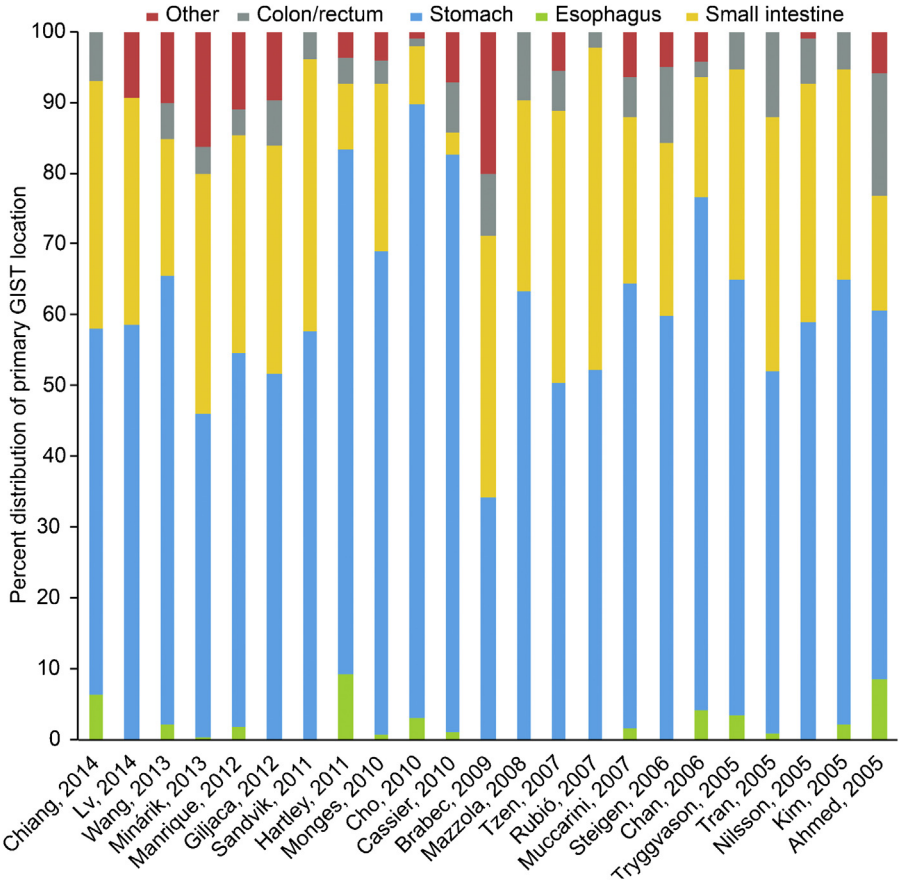

Fig. 1. Distribution of anatomical location of GIST tumors per study cohort.

USA [23]) show a very low incidence between 4.3 and 6.8 per million. However, most studies report incidences between 10 and 15 cases of GISTs per million. The majority of studies reporting an increase in incidence over time included material prior to year 2000, thus likely indicating an identification bias rather than a true increase in incidence.

The reported age ranges from 10 to 100 years, with median age reported in the mid 60s for most studies (Table 1). The gender distribution shows a fairly consistent equal distribution between male and females (Table 1).

3.2. Primary GIST location

Most GISTs are found in the stomach, and this is fairly consistently reported between studies, with some variation (Fig. 1). No clear time-trend can be found, and the variance in oesophageal and colorectal GISTs, likely both reflects the rare occurrence and possibly underreported incidence.

The collated information on localization in 9747 GISTs is presented in the Fig. 2. Gastric location is the most frequent (55.6%) followed by small bowel (31.8%), with colorectal in 6.0%, other/various locations in 5.5% and oesophagus in only 0.7% and no info in 0.2%.

3.3. Clinical presentation of primary GISTs

A total of 15 studies reported on clinical presentation, roughly split into 'symptomatic' disease (81.3%, $n = 1997$) or 'incidental' (asymptomatic, 18.7%) findings in a total of 2456 patients (Fig. 3). Data on the specific symptoms were variable recorded among the studies and with different categories and definitions used. Among the most common symptoms were noted abdominal pain, gastrointestinal bleeding and obstruction, but a number of other nonspecific complaints were reported across studies. (Fig. 3)

3.4. Distribution of size of primary GISTs

Size distribution was reliably presented in 13 studies comprising 3296 patients, for which only 102 patients did not have any information on size. As not all studies discerned between the largest size groups (e.g. not all divided the larger tumours into those >5 cm but ≤10 cm, to those >10 cm), the accumulated data are presented with 3 size groups in Fig. 4. Accumulated data showed that 49% of tumours where larger than 5 cm, and only 13% in the <2 cm size-group.

3.5. Distribution of NIH risk categories in primary GISTs

Among the studies that reported NIH risk groups (Fig. 5), the very low risk GISTs were least frequent (15%), with low, intermediate and high-risk categories representing 30%, 22%, and 33%, respectively. Only one study reported the AFIP risk category, while a number of studies reported mitosis count categories alone without attributing these findings to a risk stratum. Also, studies reported to a very variable degree if they had cases that would could not be evaluated for risk categories, such as Cho et al. who noted non-designated in 127 (10.3%) of 1227 patients.

4. Discussion

This systematic review of the available population-based studies reporting incidence and epidemiological data on GIST is the first attempt at identifying and estimating the global burden of GISTs. We report the first collective data on distribution and demographics of GISTs, as reported in the worldwide literature. The estimates of GIST incidence across regions may allow for assumptions for case accrual and recruitment for future trials and interventions.

There was a significant variation in the reported incidence of GISTs, which is likely be due to a number of factors. First, methodological issues are at hand, as the diagnostic criteria have been in development and improved over time [17,18], and, thus, variation in diagnosis and recording may have occurred. Secondly, few countries have established registries that captured all GISTs, while some cancer registries have collected data on the overt malign cases. Thus, smaller, incidental and low risk tumours may be underrepresented in several studies [54,55]. Further, studies of

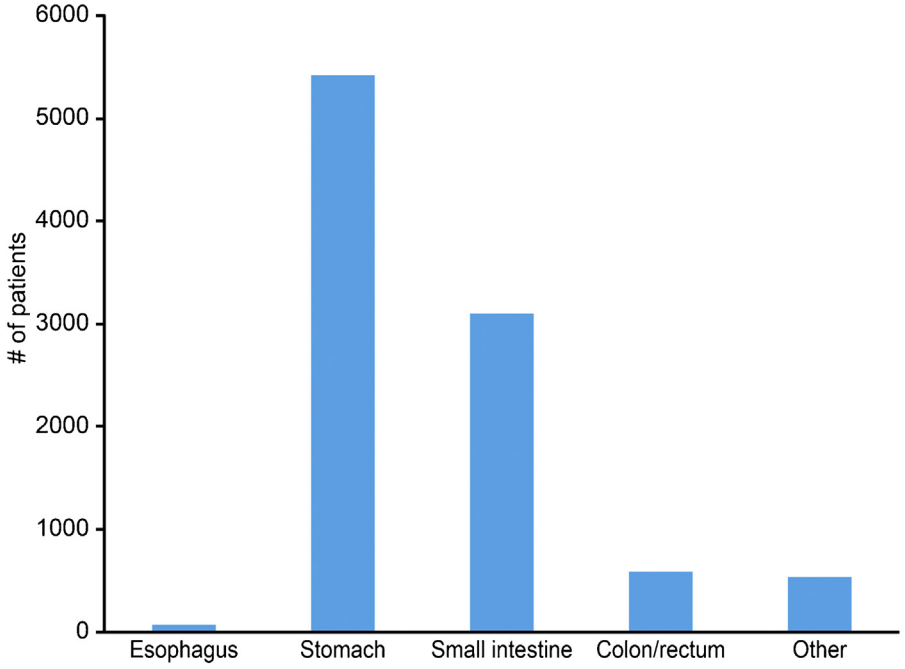

Fig. 2. Absolute number of patients with GIST per anatomical location across studies.

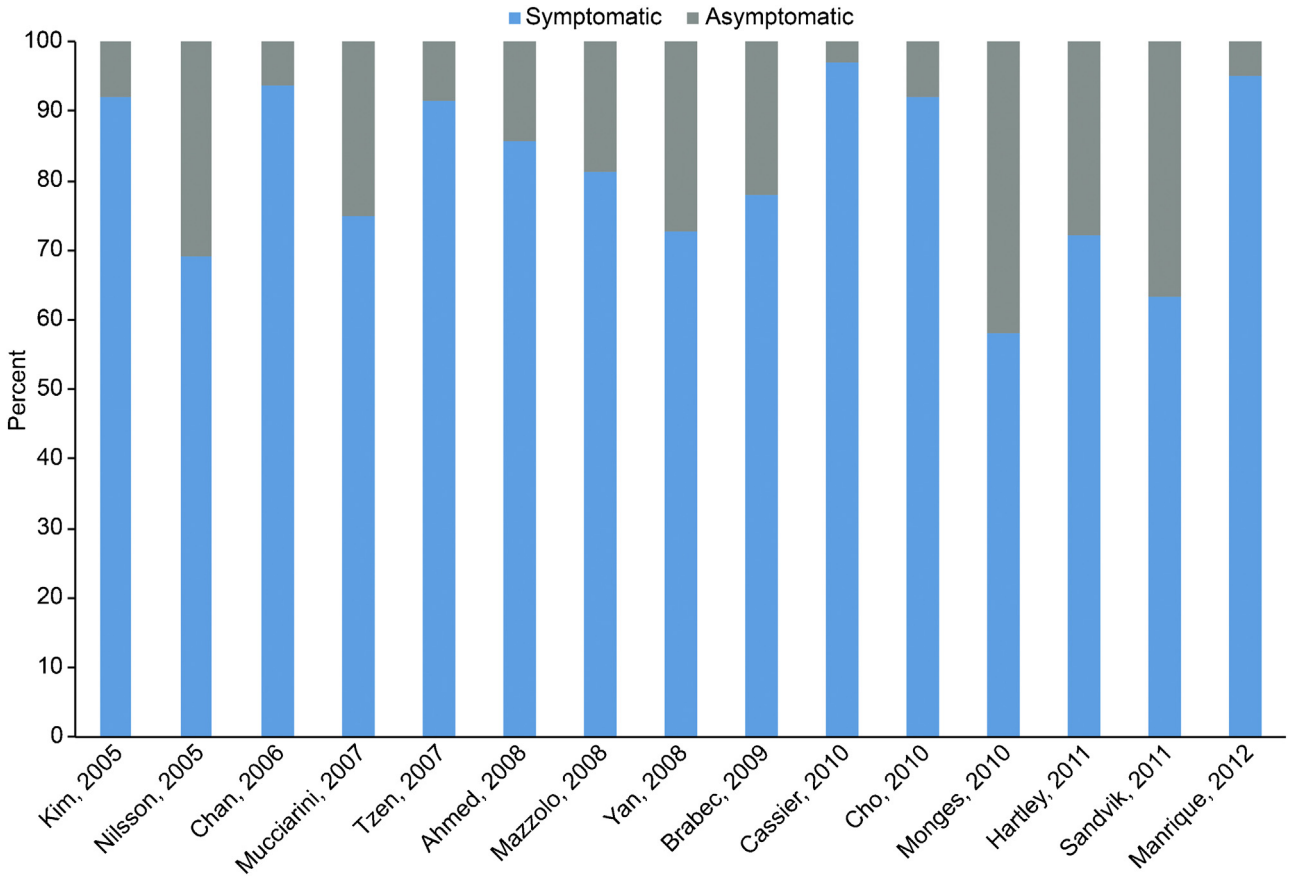

Fig. 3. Distribution of clinical presentation as symptomatic or incidental across studies.

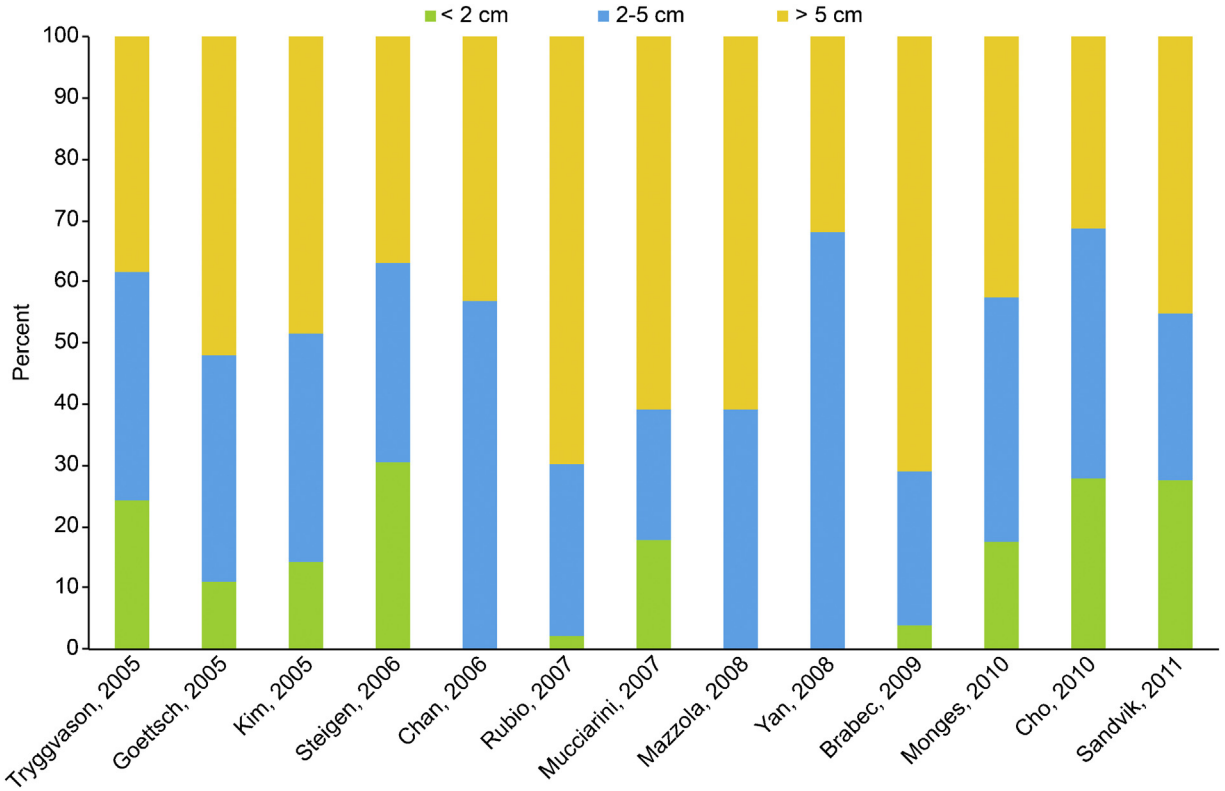

Fig. 4. Size distribution on presentation per study cohort.

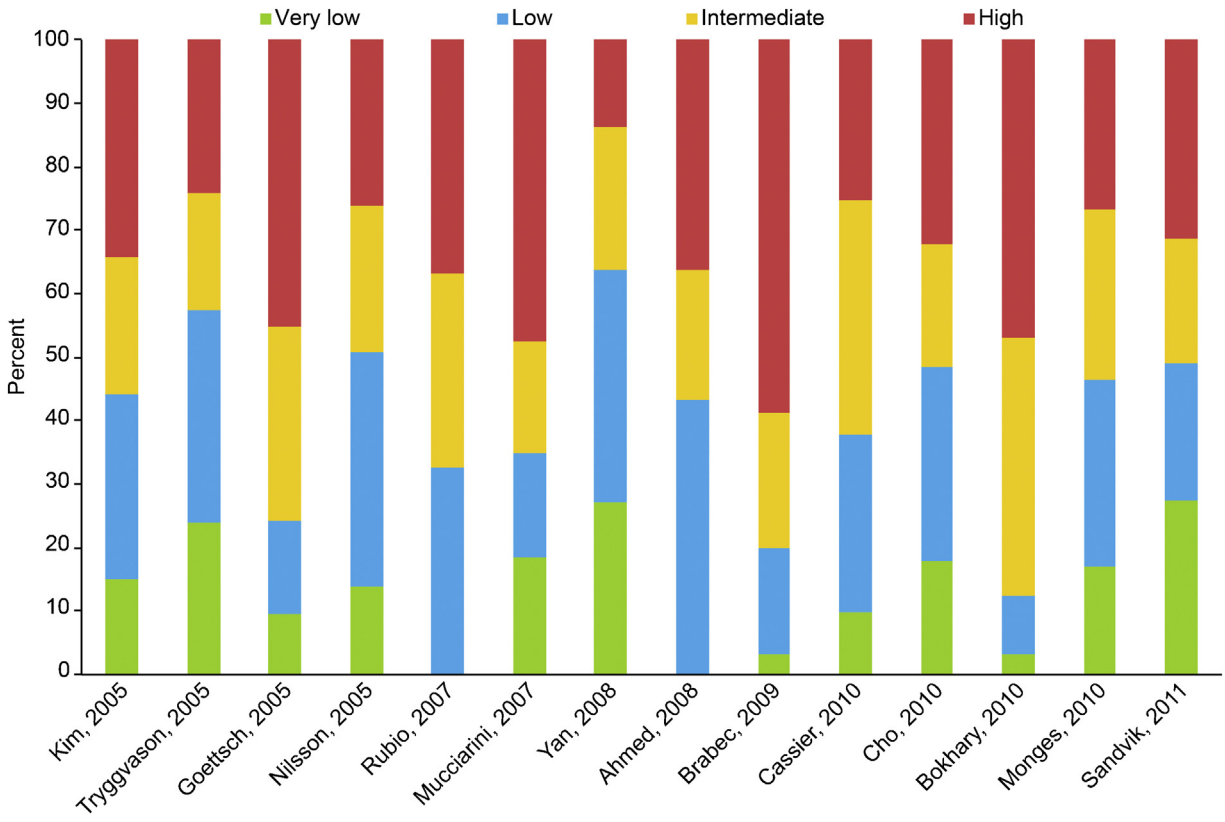

Fig. 5. Distribution of NIH risk categories per study cohort.

high-incidence from Northern-Norway [30], China (Hong Kong [31] and Shanghai [53]), and Korea [42] reported incidences up to 22 cases per million inhabitants. In contrast, data from the Shanxi province in China [48], the Czech republic and Slovakia [39], and North America (Canada [38] and USA [23]) reported very low incidences down to 4.3 per million. This 4–5-fold difference in reported incidence may be explained by differences in identification and reporting of data, for example a bias towards reporting and identification of the overtly malignant GISTs in the low-incidence reports (such as the SEER data from the US). With development and evolution of GIST specific registries [51,56–58], widespread use of the diagnostic criteria [17,18,59], use of standardized protocols [60] for reporting and more specific use of dedicated SNOMED coding, the true epidemiological collection of GIST data may prove more correct in the near future.

European data on incidence were considered conform to the reported middle values, with few outliers. Data from North America (US and Canada) did display some considerable variation, which may in part be related to reliance on SEER data that usually captures the more overt malign cases [23,24,38,61]. However, it appears that this may have improved over time, with most recent data suggesting about 8 cases per million per year, which is in line with several European studies. Not surprisingly, most studies demonstrate an increased risk and higher incidence with increasing age, with age-related incidence reported over 30 per million per year for those >70 years of age [38,61]. It should also be noted that incidental findings increase with new interventions, such as reported for gastric GISTs investigated in sleeve gastrectomies for morbid obesity, which is reaching epidemic proportions worldwide [62]. Also, in areas with population screening, such as for gastric cancer in Japan, the prognosis appears to be influenced by detection of more incidental and smaller GISTs [63]. Further, one should note that even today all diagnoses of GISTs are not readily confirmed, as only resected specimens can truly yield a sure tissue-based diagnosis. Many patients with a small lesion and a difficult location (e.g. small incidental lesion in oesophagus) may be followed by endoscopic ultrasound techniques, but tissue diagnosis may be hard to obtain or not as correct as one would like to believe [64].

The most extreme variation (from as low as 4 to as high as 22 GISTs per million per year) stems from the Asian studies reported [31,35,48,52,53]. Whether or not this represent true and unique differences or just variation in data capture or methodology remains speculative. However, it warrants further investigation into possible disease related risk differences in future studies. Obviously, the advancement in diagnostic assessment as well as outline of mutational subtypes continue to progress [18,21,65,66]. As most of the studies reported in the current collected series predated the current knowledge on mutational status and advancements in molecular classification [67,68], it was not possible to collate such information. It is expected that as methods evolve and become more widespread, such information will be more frequently reported and made readily available. Further, risk groups and prognostic tools continue to evolve and may be more readily compared across studies in the future [69,70]. Currently, adjuvant imatinib treatment has become more widespread and thus, direct comparison of survival curves over time is not justified [71,72].

Some limitations deserve mentioning in this study. First, while we attempted to contact all authors of studies where baseline info was not stated or unclear, we were unable to make contact with some authors or, they were not able to give additional needed info from their health care systems as to the epidemiological aspects of GIST. Also, several regions were underrepresented in the literature and consequently regions including several deprived and underdeveloped regions in the world, including African countries, the Middle East region, India and the South Americas were not represented with epidemiological data, although a few small

studies (non-population based) from these regions were noted in the literature [47,73–77]. Further, the heterogeneity by which studies are reported severely hampers collection of all data across studies. Thus, standard recommendations for reporting epidemiological data should be developed and adhered to in order to better collate and present high-quality data for comparison. While GIST is perceived to be a rare disease, it remains the most frequent mesenchymal tumour of the digestive tract. Further, GIST patients have had a notable increase in prevalence due to the progress in surgical and oncological management. Estimates suggest that the prevalence is over 10-times that of the incidence, with GIST-survivors now being in the number of 135–155 per million per year in several studies [26,31,78].

5. Conclusions

This collective review of population-based epidemiological reports on GIST confirms several features, such as a fairly equal gender distribution, predominant age in the 60s, over 80% present with symptoms, and tumours most frequently located in the stomach and small bowels. The rather large tumour size and high risk grade reported may point to a bias in selection and recording of tumours with unfavourable appearance, possibly understating the true incidence of smaller and more "innocent tumours" [55]. The variable incidence across regions warrants further investigation into differences in methodology or true population difference in disease risk. Future reports should strive to standardize reporting according to uniform diagnostic and prognostic criteria.

Conflicts of interest

None declared by any of the authors.

Financial disclosures

None of the authors have any financial disclosures to make regarding the eventual acceptance and publication of this study.

Author contribution

KS planned the review.

KS, OMS, JAS did the initial literature research. VG, AJ, VRB did additional searches. AJ provided main data and translation from Chech registry numbers. All authors contributed to data extraction, interpretation of numbers and analyses. KS drafted the initial manuscript. All authors contributed to several rounds of revisions. All authors have read and approved the final version of the manuscript.

Acknowledgement

We appreciate the time given by those authors who were able to respond to our queries for this study.

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