Low Socioeconomic Status is a Risk Factor for Delay to Treatment and Mortality of Testicular Cancer Patients in Hungary. A Prospective Study

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Keywords: testicular cancer, socioeconomic status, patient delay, doctor’s delay

DOI: https://doi.org/10.21203/rs.3.rs-273912/v1

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Abstract

Background. In Hungary, the mortality rate for testicular germ cell cancer (TGCC) is 7.6% which is significantly higher than the EU average. We prospectively evaluated the effect of socioeconomic status on patient delay, doctor's delay, and therapy outcomes.

Methods: Questionnaires on subjective (MacArthur Subjective Status Scale), objective (wealth, education, and housing data) social status, and on patient's and doctors' delays were completed by newly diagnosed TGCC patients.

Results: Patients belonged to a relatively high socioeconomic class, a university degree was double the Hungarian average, Cancer-specific mortality in the highest social quartile was 1.56% while in the lowest social quartile 13.09% (p=0.02). In terms of patient delay, 57.2% of deceased patients waited more than a year before seeking help, while this number for the surviving patients was 8.0% (p=0.0000). Longer patient delay was associated with a more advanced stage in non-seminoma but not in seminoma, the correlation coefficient for non-seminoma was 0.321 (p<0.001). For patient delay, the most important variables were the mother's and patient's education levels (r=-0.21, p=0.0003, and r=-0.20, p=0.0005), respectively. Since the patient delay was correlated with the social quartile and resulted in a more advanced stage in non-seminoma, the lower social quartile resulted in higher mortality in non-seminoma patients (p=0.005) but not in seminoma patients (p=0.36) where the patient delay was not associated with a more advanced stage.

Conclusions: Based on our result, we conclude that to improve survival, we should promote testicular cancer awareness, especially among the most deprived populations, and their health care providers.

Background

Malignant testicular germ cell cancer (TGCC) is relatively uncommon, however, this is still the leading type of cancer in men between the ages of 20 and 40 years. [1] Due to huge improvements in imaging and chemotherapy, mortality rates in patients with testicular cancer have declined in recent decades. In the most affluent world regions, while rapid increases in incidence rates have been observed lately, the mortality rates declined to 0.2–0.3 per 100,000. However, in Central and Eastern European (CEE) countries (i.e., Bulgaria, Czech Republic, Hungary, Poland, Romania, and Slovakia), rates have only moderately declined and were still 1.3/100,000[2][3][4] for men aged between 20 and 44 years in 1995–1997. In the first decade of the 2000s, a significant decline in testicular cancer patients’ mortality rates appeared also in CEE countries, but the ratio is still higher than in the more developed EU members. [5] According to a WHO database, Hungary and Latvia had the worst TGCC mortality rate in Europe (0.9/100,000) between 2000 and 2006.[6]. The slower and delayed declines in the less developed, lower resource countries imply that the high cost of appropriate treatments together with inadequate patient referral systems are responsible for the high mortality rates and less favorable trends. Another factor of the slower progress may partly relate to differences in socioeconomic status (SES), i.e. men with lower SES may be
characterized by a lack of awareness and maybe less likely to seek immediate medical help, moreover, they tend to have the worst access to medical service, particularly in rural and remote communities. There is extensive literature describing SES differences and cancer survival in countries around the world in various health care systems. [7][8][9][10]

The authors of this report prospectively evaluated the effects of subjective social status (SSS) on delay to diagnosis, stage distribution, and cancer-specific mortality (CSM) in men with TGCC. The studied patient cohort was treated at the National Institute of Oncology GU department, which is the main germ cell cancer center in Hungary, treating roughly 60% of the approximately 600 Hungarian TGCC patients yearly.

The aim of this research was to investigate how the patients’ socioeconomic status affects the time elapsed between onset of symptoms and diagnosis, and therapy outcome.

Methods

2.1. Ethical statement

This prospective, non-interventional study was carried out between January 2016 and January 2018, at the National Institute of Oncology. The database lock occurred in September 2019. The study was performed in accordance with Hungarian laws and regulations and was approved by the Hungarian National Scientific Ethical Committee (approval number: 44476-2/2016), and as per the standards of the World Medical Association Declaration of Helsinki. All patients who were willing to participate signed informed consent.

2.2. Study population

Inclusion criteria included male patients over 16 years old (inclusive), with newly diagnosed testicular cancer with a gonadal onset.

Clinical stage and prognosis were determined according to the Union for International Cancer Control (UICC), [11] and the International Germ Cell Cancer Collaborative Group (IGCCC) [12] based on the pathology report, the tumor marker (AFP, HCG, LDH) level, and the CT scan. Castration was the first-line treatment for the majority of patients (Table 1), followed by surveillance or adjuvant chemotherapy (St I), or by multiple cycles of platinum-based chemotherapy, and salvage surgery where needed (St II-III). In 16 patients whose conditions related to metastatic dissemination required immediate chemotherapy, orchiectomy was postponed until the completion of chemotherapy. Patients received the internationally recognized standard of care, based on the current European Society for Medical Oncology (ESMO) guideline.[13]

2.3 Assessment of the objective and subjective socioeconomic status
The subjective social status (SSS) and objective socioeconomic status (SES) questionnaires were completed on the first consultation visit of newly diagnosed TGCC patients. The SSS was determined based on the MacArthur Scale of Subjective Status questionnaire. After the owner’s written permission for usage and linguistic validation, the questionnaire has been translated into Hungarian and was adapted for this study. MacArthur scale is a social or community hierarchy ladder used by the patients based on their deemed place; with values of 1–10. [14][15][16][17] We measured two variables: social status, and community status value (Fig. 1). For objective SES patient’s highest educational attainment, residency, income, possession of consumer durable goods, occupational class, and the parents’ highest educational level were evaluated. An index number was created based on the educational level, the number of consumer durable goods, and the size of living area per capita. Based on this index number, patients were divided into 4 quartiles. The first quartile was the lowest, with the poorest status and lowest educational level. The section on illness comprised of questions including the time gap between the first symptoms and visiting a doctor (patient delay, PD), and between the first doctor’s visit and first consultation at our institute (doctor’s delay, DD). Histology, stage, and treatment outcome were extracted from the patient database.

2.4. Statistical analyses

Statistical analyses were performed using SPSS 22.0 (IBM Corp.) and Statistica 12.5 (StatSoft, Tulsa, OK, USA). To detect the association between the doctor’s delay and overall survival (OS) Mann-Whitney U test was used while the correlation between the patient’s delay and survival was determined by logistic regression. To examine the effect of SES on survival Fisher exact test was carried out. The association between various patient characteristics and OS were analyzed by Kaplan-Meier analysis. To examine the correlation between patient education and PD, and between SSS and SES, Spearman rank correlation was performed. Results were considered significant at p values lower than 0.05.

Results

3.1. Patient characteristics

Altogether, 306 patients filled out the questionnaire. Analyses were performed on 303 patients who met the inclusion criteria (3 cases with non-gonadal origin were excluded from the analysis). The patients’ mean age was 35.9 years (seminoma 38.5, non-seminoma 33.1) (Table 2). The mother’s mean age at childbirth was 26 years whilst the father’s mean age at childbirth was 29.1 years. Patients belonged to a relatively high socioeconomic class, 103 (34%) patients had a university or college degree, which is twice as many as the Hungarian society average. [18] SSS among patients was 5.57 ± 1.70 while the Hungarian average among males in this age group is 3.97 ± 0.03 (out of 10). [19] Fourteen patients died during the study period, they were significantly older than the surviving patients, 41.6 vs. 35.9 years (p = 0.0277) (Table 1). Among patients with metastatic seminoma 152 (98.7%) belonged to the good and 2 (1.3%) to the intermediate prognostic group, while among those with non-seminoma 116 (77.9%), 12 (8.0%), and 21 (14.1%) belonged to good, intermediate and poor prognostic group, respectively. Table 3 shows the stage
distribution among seminoma and non-seminoma patients. The majority of patients belonged to stage I (seminoma: 71.5% and non-seminoma 47.6%), though a higher proportion of non-seminoma patients had metastatic disease (StII/StIII) at diagnosis (28.5% seminoma vs. 52.4% non-seminoma).

3.2. Objective and subjective social status

Regarding patients’ residence type, distance from the National Institute of Oncology, number of household members, number of members with income, and internet usage frequency there was no difference between the seminoma and non-seminoma group (Table 2). Table 4 presents social quartiles based on objective social status and the distribution of SSS. The distribution of SSS was normal (Table 4). The full range of score distribution (1–10) was observed. The mean SSS value for the entire sample was 5.57 ± 1.70, while the median and mode coincided between the fifth and sixth rung. In terms of SSS, there was also no difference between seminoma and non-seminoma patients (p = 0.7898).

3.3. Patients’ objective versus subjective self-grade values

The patient’s SSS was compared to the SES indicators. Both the social ladder value and the community ladder value exhibited a significant correlation with the objective socioeconomic status-based quartiles (r = 0.508 and r = 0.417, respectively, p < 0.001).

3.4. Factors associated with patient’s delay and doctor’s delay

The diagnostic time path was from within 1 week to over 1 year, with the ‘1 week-1 month’ being the median (102 patients). We found a negative correlation between the father’s education and patient delay (PD) (r=-0.12, p = 0.0383), and an even stronger negative correlation between the mother’s education and the PD, as well as the patient’s education and the PD (r=-0.21, p = 0.0003, and r=-0.20, p = 0.0005, respectively). Table 5 shows PD based on the educational level of the patients. Both PD and DD negatively correlated with social quartile (r=-0.18, p = 0.0022 and r=-0.15, p = 0.0131, respectively). The social quartile value showed a stronger association with PD than with DD, the latter also correlated with the distance (km) from the National Institute of Oncology (r = 0.12, p = 0.0347). Each PD and DD were significantly longer for deceased patients than for surviving patients (Table 6).

3.5. Patient delay, social quartile, and overall survival

Of the 14 patients who died during the study course, 11 (78.6%) were in the social quartile 1 (lowest), compared to 73 of the 289 surviving patients (25.3%) (p < 0.001) (Table 5) Fig. 2 shows the OS based on the social quartile, and PD for all patients and separated for non-seminoma and seminoma patients. 57.2% of deceased patients waited more than a year before seeking help, while this number for the surviving patients was 8.0% (p < 0.001). Longer PD was associated with a more advanced stage in non-seminoma, but not in seminoma patients, the correlation coefficient for NS was 0.321 (p < 0.001) hence PD significantly influenced OS in NS (p = 0.0021) but not in S (p = 0.13) (Fig. 2). Since PD was correlated with social quartile, as mentioned above, and resulted in a more advanced stage in non-seminoma, lower
social quartile resulted in higher mortality in NS patients ($p = 0.0048$) but not in S patients ($p = 0.36$) where PD was not associated with more advanced stage.

**Discussion**

The present study has been conducted at one site (National Institute of Oncology, Department of Genitourinary Medical Oncology and Clinical Pharmacology), between 2016 and 2018, and includes the prospective data analysis of the socioeconomic status of patients followed or treated with testicular cancer. The 303 patients who participated in the study, is approximately half of the yearly Hungarian TGCC incidence (600–650 cases/year). [20]

Inequalities in cancer mortality and morbidity between populations with different (lower and higher) socioeconomic positions are widely described in the literature [21]. We measured both the subjective (social ladder, SSS) and objective (SES) social status and found that both the social ladder value and the community ladder value exhibited a significant correlation with the objective socioeconomic status-based quartiles. The association between SES and SSS, which is distinctive in different cultural groups, was reported in several papers.[22] [23][24] SSS is easier to use because many people do not want to report their income and education levels. Furthermore, it seems to predict health and general well-being better than objective SES measurements. [17][25]

In the current study, we found a major deviation in terms of the patient’s highest education level compared to the country averages Those educated to college/university level (34%) were represented 1.5 times more as the Hungarian society averages suggest, while those with the lowest education (8%) have been presented in a significantly lower extent compared to the Hungarian average (27%). [18] SSS among patients was 5.57 ± 1.70 while the Hungarian average among males in this age group is 3.97 ± 0.03 (out of 10). [19] Numerous reports indicate that TGCC has for some time tended to occur disproportionately among men of high socioeconomic status and the sons of women of high socioeconomic status [26][27], while other reports have not found such associations [28].

Since both the intensity of treatment and prognosis are based on the extent of disease at presentation, a testicular cancer diagnosis must not be delayed. Among our TGCC patients, PD and DD showed significant relations with social status. In terms of PD, the most influential was the mother's and patient’s education. Delay in the diagnosis of testicular cancer is well documented [29][30][31][32]. Dieckmann and colleagues found that PD was related to educational level. College-educated men were found to have shorter mean and median delay [33] [25]. The less educated patients may actually believe that a larger testicle makes a more virile man. [34]. On the other hand, Toklu et al. have not found a correlation between the annual income, the educational level, and the delay to treatment [35][26]. Physician-mediated delay most commonly results from the misdiagnosis of a testis tumor as an infection. In one study of 335 testicular cancer patients, one third were treated initially with antibiotics for presumed epididymitis[31]. In our cohort social quartile value showed a stronger association with PD than with DD, the latter also correlated with the distance (km) from the National Institute of Oncology.
There is only a limited reference in the literature to the possible association between the patient’s SES and the stage of their disease. Seminomas can have an indolent growth, and delay in diagnosis usually does not result in a more advanced stage. [34][32][36] Since in our study PD in seminoma patients did not influence the stage, thus the social quartile in seminoma did not determine the survival significantly. For non-seminoma patients, there is a clearer association between delay in diagnosis and advanced disease. [30] [31][37][38] and the increased delay has also been associated with decreased survival [34][36][39]. PD among our non-seminoma patients presented a more advanced stage, and based on our research, PD was significantly correlated with social status, therefore social quartile and survival also had significant interdependence in non-seminoma patients. In the study of Davies, TGCC patients with lower SES had higher mortality rates. [40]. Sun et al. reported from their multivariate analysis that low SES groups had significantly higher cancer-related mortality rates, as well as higher collective mortality rates retrospectively.[41] This was in line with the findings of Davies et al. who reported a higher mortality rate among those educated at the vocational school level.[40] This has also been proved by the results reported in this research, as 10 out of 14 deceased patients were educated to that level, and 9 out of 10 belonged to the lowest quartile. The number of deceased patients was significantly higher among those who waited at least 1 year before the first doctor visit. According to our knowledge, there is no similar finding, published in our research area.

The mortality rate among our patients (4.6%) was better compared to the Hungarian average (7.6%), and this underscores the importance of having the TGCC patients managed in a specialized center, It has been reported earlier that specialist centers demonstrate superior results to nonspecialist centers [42][43]

Limitation of the study

Similar to other studies measuring patient-reported timelines, bias may occur when patients recall the exact delay period.

Conclusions

To our knowledge, this is the first study that prospectively evaluated the TGCC patients’ objective and subjective social statuses along with survival ratios, all other studies investigated them retrospectively, and indirectly. Mother’s and patient education posed an influential aspect of PD; higher education led to a shorter PD period and hence better survival in non-seminoma patients.

Based on our result, we conclude that to improve survival, we should promote testicular cancer awareness, especially among the most deprived populations, and their health care providers.

Abbreviations
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<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AFP</td>
<td>Alpha-fetoprotein</td>
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<td>CEE</td>
<td>Central and Eastern European countries</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>CSM</td>
<td>Cancer-specific mortality</td>
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<td>DD</td>
<td>Doctor's delay</td>
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<td>EU</td>
<td>European Union</td>
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<td>GU</td>
<td>Genito-urinary</td>
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<td>HCG</td>
<td>Human chorionic gonadotropin</td>
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<td>IGCCCG</td>
<td>International Germ Cell Cancer Collaborative Group</td>
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<td>Km</td>
<td>Kilometer</td>
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<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<td>OS</td>
<td>Overall survival</td>
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<td>PD</td>
<td>Patient delay</td>
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<td>SES</td>
<td>Socioeconomic status</td>
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<td>SSS</td>
<td>Subjective social status</td>
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<td>St</td>
<td>Stage</td>
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<td>TGCC</td>
<td>Testicular germ cell cancer</td>
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<td>UICC</td>
<td>Union for International Cancer Control</td>
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<td>WHO</td>
<td>World health organization</td>
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**Declarations**

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**Contributions:**

Zs.K, and K.B planned and conducted the research with the help of T.M. Statistical analysis was carried out by G.F and Á.K. The SSS and SES questionnaires were created by A.T. Critical revision was carried out by A.L. All the remaining authors (L.G, F.Gy, O.H, G.K, T. D, E.L, K N.) helped with data collection. All authors have read and approved the manuscript.

**Ethics approval and consent to participate:**

The was approved by the Hungarian National Scientific Ethical Committee (approval number: 44476-2/2016). All patients who were willing to participate signed informed consent.

**Consent to publication:**

Not applicable

**Competing interests**

We declare that we have no conflict of interest.

**Funding:**

Not applicable
Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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