Suicides and deaths linked to risky health behavior in childhood cancer patients

- **a Nordic population-based register study**

Short running title:

Risky health behavior related deaths

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Precis for use in the Table of Contents:

Childhood cancer patients appear to have an increased risk for risky health behavior related causes of death compared to the general population.

The overall risk for suicide was also found to be elevated, significantly when cancer was diagnosed between age 15 and 19 years.

Abstract:

Childhood cancer survivors have been reported to be vulnerable to psychiatric morbidities and risky health behavior. Suicides, substance abuse, accidents and violence as causes of death can be regarded as an extreme manifestation of risky health behavior. We studied the risk for suicide and other risky health behavior related deaths among childhood cancer patients in Denmark, Finland and Sweden. By linkage between national cancer, population and cause of death registries, we investigated the causes of death in 29,285 patients diagnosed with cancer under the age of 20 years between 1971 and 2009, compared with a cohort of 146,282 age-, sex- and country-matched population comparisons. Rate ratios (RRs) with 95% confidence intervals (CIs) were estimated using Poisson regression models, adjusting for demographic factors. The overall risk of dying a risky health behavior related death was increased among childhood cancer patients (RR 1.25, CI 1.06 – 1.47) when compared with population comparisons. The elevated risk was statistically significant among CNS tumor patients (RR 1.49, CI 1.08-2.05) and patients diagnosed at 5-9 and 15-19 years of age (RR 1.50, CI 1.01-2.24; RR 1.31, CI 1.03-1.67, respectively). The overall risk for suicide was increased (RR 1.37, CI 1.02 - 1.83), statistically significantly when diagnosed between 15 and 19 years (RR 1.61, CI 1.09 - 2.39). Childhood cancer patients appear to have an increased risk for risky health behavior related causes of death compared to the general population. Our results imply the importance of integrating psychosocial support in the follow-up care of childhood cancer survivors.

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Introduction

Survival of childhood cancer patients has improved considerably over the last four decades, with 5-year survival rates exceeding 80% in most of Europe (1, 2). The improvements in outcome, however, have come at a cost of long-term sequelae, with a majority of survivors developing a chronic health condition within 30 years of diagnosis (3, 4).

It has been shown among adult survivors of childhood cancer that it is not only the original cancer diagnosis but also the quantity and severity of chronic conditions that particularly contribute to diminished health-related quality of life (5). These adverse late effects of childhood cancer are not limited to somatic health problems as diagnosis, treatment and somatic conditions may also affect the psychosocial trajectory of childhood cancer survivors throughout their lifetime (6).

A Danish study reported an increased risk of hospital contacts for mental disorders in childhood cancer survivors when compared with population-based comparisons (7). These findings were further supported by a study from Finland, in which female survivors were found to have a significantly higher risk for anxiety or neurotic disorders, personality disorders, somatization or eating disorders, psychotic disorders and depression, when compared with female siblings (8).

Suicides, alcohol and drug abuse, accidents and violence as causes of death can be regarded as an extreme manifestation of risky health behavior. Findings from the Swiss Childhood Cancer Survivor

Study indicated that childhood cancer survivors engage in binge drinking and consume alcohol more frequently than the general population (9). There is also evidence that childhood cancer survivors harbor suicidal intentions (10) and have progressive psychoactive medication use (11, 12) when compared with siblings and population comparisons.

Less than 20% of survivors report having received follow-up care that included advice about risk reduction (13, 14). As suicides and injuries are among the leading causes of death in young people worldwide (15, 16), and as psychiatric morbidities seem to be overrepresented among childhood cancer patients (6) there is a genuine need to evaluate whether childhood cancer patients are at an elevated risk for suicide or other risky health behavior related deaths.

The aim of this three-country-wide cohort study was to assess whether childhood cancer patients are at an increased risk of risky health behavior related deaths. Using information obtained from the unique Nordic registries, we investigated causes of death, namely suicides and deaths due to accidental, violent, alcohol or drug abuse related causes during follow-up in childhood cancer patients compared to population-based comparison subjects and aimed at identifying patients at particular risk for these adverse outcomes.

Materials and Methods

This study is part of the Socioeconomic Consequences in Adult Life after Childhood Cancer in Scandinavia (SALiCCS) research program (www.saliccs.org), which is a large registry- and population-based retrospective cohort study investigating various socioeconomic consequences and family characteristics in childhood cancer survivors from Denmark, Finland and Sweden.

Denmark, Finland and Sweden have civil registration systems (17, 18, 19) with various national population-based administrative registries providing individual level information on a variety of outcomes such as cancer and causes of death. Every Nordic citizen is assigned a unique personal

identity code that is used in all national registries, enabling accurate linkage of information between registries. The Nordic legislation permits and supports registry-based research (20). Data linkage between these registries provided the basis for this Nordic population-based cohort study.

Study cohort

Our study population included 29,285 cancer patients diagnosed with cancer in Denmark, Finland and Sweden before the age of 20 years between 1971 and 2009 and 146,282 population-based comparison subjects (1:5 ratio) identified from the respective national population registries and matched by birth month and year, sex and country. Comparison subjects had to be alive on the date of cancer diagnosis of the corresponding patient and free of early onset cancer (diagnosed under 20 years of age). Characteristics of the cancer patient cohort are displayed in Table 1.

Childhood cancer patients were identified from the national cancer registries in the respective countries including information on cancer diagnosis. Reporting new cancer cases to national cancer registries is obligatory in the Nordic countries and the coverage of registries is thus virtually complete (21, 22).

Information on causes of death was obtained from the national cause of death registries (23, 24, 25) and causes of death were classified according to the International Classification of Diseases (ICD) with different versions used in the three countries during the study period (Supplementary Table 1). The respective codes were harmonized between countries and merged into one large Nordic dataset for analyses.

The underlying cause of death was identified for all deceased patients and comparison subjects. The underlying cause of death was defined as the disease that initiated the series of conditions leading directly to death, or the circumstances connected with an accident or an act of violence that caused the injury leading to death. We divided the underlying causes of death into those with a medical cause

and those with an external cause of death according to the ICD and further classified them into subgroups (Supplementary Table 2).

We then went on to identify all causes of death related to risky health behavior, defining them to include external causes of death (suicide, transport accidents, drowning, assault, accidental poisoning and other accidents) and deaths caused by diseases related to alcohol or drug abuse (Supplementary Table 2). Accidents due to complications of medical or surgical care were excluded. Alcohol and drug abuse were further sub-divided into accidental poisonings and diseases related to alcohol and drug abuse. In addition to the underlying causes of death, cause of death registers comprise additional causes, such as contributory and immediate causes of death. We have used only underlying causes of death due to inconsistencies in the availability of additional causes.

The data were based on national registry linkage and no contact was made with the families. The study was approved either by the Danish Data Protection Agency, the Finnish National Institute for Health and Welfare, Statistics Finland or the Swedish Regional Ethical Review Board in the respective countries (Denmark: 2014-41-3032; Finland: THL/1342/5.05.00/2015, TK53-358-16 and Sweden: DNR: 2016/25-31/5).

Statistical analyses

We calculated the accumulated person-years at-risk for patients and comparisons and identified the numbers of deaths in different groups of underlying cause of death. Follow-up began at date of cancer diagnosis for cases and from the equivalent age for matched comparisons and ended at death, emigration, or the end of follow-up (Denmark and Sweden: 31st of December 2008, Finland: 31st of December 2012), whichever occurred first.

We estimated rate ratios (RR) with 95% confidence intervals (CIs) using Poisson regression modelling with person-years as a model offset. Analyses were adjusted for country, sex, attained age and diagnostic period (diagnosis within 1971-1979, 1980-1989, 1990-1999 or 2000-2009). We performed sensitivity analysis incorporating matching as a random effect in the hierarchical Poisson regression model. Models were fitted with bmrs (Stan-program interface) package in R. The results and conclusions were comparable to those reported here, i.e. from unmatched analysis.

Cancer diagnoses were classified according to the 12 main diagnostic groups of the International Classification of Childhood Cancer (ICCC-3) (26). Due to the small number of cases in some diagnostic groups, we analyzed leukemia, lymphoma and central nervous system (CNS) tumors separately and combined all other cancer diagnoses into one group (non-CNS solid tumors). Comparison subjects were assigned into the same cancer stratum as their index patient.

We also conducted analyses stratified by diagnostic age (with categories: 0-4 years, 5-9 years, 10-14 years, and 15-19 years) to take into account the similarity of diagnostic distribution and treatment regimens by age. Similarly, we present analyses stratified by sex, country, diagnostic time period, follow-up time, and attained age. Stratified analyses were conducted for all risky health behavior related causes of death combined and for suicides separately.

Statistical analyses were conducted using the statistical program R (version 3.5.1).

Results

The median follow-up time was 9.4 years (range 0-42.0 years) and 18.1 years (range 0-42.0 years) for cancer patients and for comparisons, respectively. The median age at the end of follow-up was 19.0 years (range 0-59.1 years) for cancer patients and 27.4 years for comparisons (range 0-58.8 years). In all, 32.5% of childhood cancer patients and 1.3% of comparison subjects had died by the end of follow-up. Cancer was the underlying cause of death for 90.3% of the patients and for 10.3%

of the comparisons (Supplementary Table 2). As this is a comparatively young population with low mortality rates in the comparison group, external causes of death were the most common underlying causes of death among comparisons, comprising 52.1% of deaths. Suicide was the underlying cause of deaths in 17.1% in this group. For childhood cancer patients, with overall considerably higher mortality rates, 1.6% of the deaths were due to external causes, and 0.6% due to suicide. The risk for dying of external causes was significantly increased among cancer patients when compared with comparison subjects (RR 1.29, 95% CI 1.09 - 1.53) (Supplementary Table 2).

Risky health behavior related causes of death

The overall risk for dying of risky health behavior was significantly increased among cancer patients when compared with comparison subjects (RR 1.25, 95% CI 1.06 – 1.47). The risk was similarly elevated in male and female patients compared to comparison subjects of the same sex (Table 2).

In cause specific analyses, we observed an increased risk for dying of alcohol poisoning and suicide among cancer patients compared with comparison subjects (RR 2.83, 95% CI 1.28 - 6.27; RR 1.37, 95% CI 1.02 - 1.83, respectively) (Supplementary Table 2).

In analyses stratified by age, we found statistically significant elevations in the risk for dying of risky heath behavior related causes in patients diagnosed at 5-9 and 15-19 years of age (RR 1.50, 95% CI 1.01-2.24; RR 1.31, 95% CI 1.03-1.67, respectively) and at an attained age of 30-39 years (RR 1.50, 95% CI 1.07 – 2.09).

In analyses by cancer type, we found a statistically significantly increased risk for risky health behavior related death in CNS tumor patients only (RR 1.49, 95% CI 1.08-2.05), when compared with population comparisons (Table 2).

Suicide

The risk of committing suicide was statistically significantly increased among cancer patients when compared with comparison subjects (RR 1.37, 95% CI 1.02 - 1.83). No statistically significant difference by sex was found (p=0. 47).

In Finland and Sweden, the slightly elevated risk for suicide was not statistically significant (RR 1.18 95% CI 0.74 - 1.86; RR 1.32 95% CI 0.81 – 2.14, respectively). In Denmark, the risk for suicide was statistically significantly increased among cancer patients when compared to comparison subjects (RR 2.05, 95% CI 1.12 - 3.74). The difference between countries, however, was not statistically significant (p = 0.42).

When looking into the effects of diagnostic period, the increased risk of suicide among cancer patients was only observed in those diagnosed and treated in the time period of 1971 – 1979 and 1990 – 1999 (RR 1.56, 95% CI 1.00 – 2.43; RR 1.79, 95% CI 1.01 – 3.18, respectively).

Stratifying by diagnostic age, we observed the risk of suicide to be increased when cancer was diagnosed between 15 and 19 years (RR 1.61, 95% CI 1.09 - 2.39). Due to low numbers, statistical power was insufficient to conduct further stratified analyses (Table 2).

Discussion

In our population-based retrospective cohort study of nearly 30,000 patients and over 145,000 comparison subjects from Denmark, Finland and Sweden, we found that childhood cancer patients were at an increased risk for deaths related to risky health behaviors. CNS tumor patients and patients diagnosed at 5-9 and 15-19 years of age were particularly vulnerable for these outcomes. In this three-country-wide setting, we also observed a statistically significant risk for suicide among cancer

patients compared to comparisons. The risk was increased for those diagnosed between 15 and 19 years of age.

Our results concerning suicides show most marked risk elevation in the Danish population, where the risk for suicide was two-fold in cancer patients compared with comparisons. These results are in concordance with the ones previously reported from Norway, where a 2.5-fold risk of suicide was found in cancer patients diagnosed before the age of 25 years when compared to cancer-free comparison subjects (27). The Norwegian study, however, did not find any risk elevation for external non-suicidal causes of death, whereas we found a significantly elevated risk for these causes in our data (RR 1.25, 95% CI 1.01 – 1.54, data not shown). Compared with the Norwegian study, our cohort consisted of younger patients and comparisons and our follow-up time was longer. Moreover, the Norwegian study began follow-up for non-suicidal violent causes of death at the age of 15 years, whereas we did not have such restrictions in our study (27).

In the North American Childhood Cancer Survivor Study cohort, adult survivors of childhood cancer had more suicidal ideation when compared with siblings (10). However, unlike our findings where the overall risk for suicide was increased among cancer patients when compared with comparisons, the rates of suicide were found to be at the level of the general population (10). A publication from the British Childhood Cancer Survivor Study showed a standardized mortality ratio (SMR) of 1.2 (95% CI 1.1-1.4) for death due to all external causes, suicide included, which is in line with our results (28).

Among adult cancer patients, risk of suicide has been found to be highest during the first year after cancer diagnosis (29, 30). In our study, we found a similar pattern, although due to the rarity of suicides in the childhood age group, our results were not statistically significant. Due to the low number of suicides, we could not find a specific follow-up time period with a more pronounced risk elevation. One possible explanation for the difference between our results and those of previous studies could be that the majority of patients in our cohort were so young at the time of cancer

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diagnosis that this type of outcome is an extreme rarity. Moreover, most of the long-term disadvantages do not emerge before early adulthood, when patients have to live independently for the first time.

Dying of accidents, violence or suicide can be regarded as the tip of the iceberg of risky health behavior. In a Swedish population-based registry study, Lu and colleagues explored both suicide attempts and completed suicides among cancer patients diagnosed between the age of 15 and 30 years, and found a 1.6-fold increased risk for suicidal behavior when compared with cancer-free comparisons, the risk being 2.5-fold increased during the first year after diagnosis (31). The risk for a completed suicide was 4-fold increased within one year after diagnosis when comparing cancer patients with cancer-free comparisons (31). In our study, we did not have data on suicide attempts or milder manifestations of risky health behaviors. Studies with information regarding hospitalizations for such conditions are needed to explore subgroups of patients who would benefit the most from psychosocial support. There is also a possibility that some cases of suicides are misclassified as accidents in cause of death registers. That is one reason why we wanted to explore suicides and risky health behavior related deaths both together and separately. (32)

Previously, Ahomäki et al. have found that survivors diagnosed with a CNS tumor in childhood are at an increased risk for various psychiatric disorders when compared with siblings (8). CNS tumor survivors overall are at high risk for poor psychological adjustment, at least partly due to CNS-directed therapies (6). In studies exploring suicidal ideation and suicides among childhood cancer survivors, patients with brain tumors have been particularly vulnerable to develop these outcomes. (27, 33, 34) Our results indicate an elevated risk for death resulting from risky health behavior related causes among CNS tumor patients. The psychological burden caused by excess psychiatric morbidity could expose patients with CNS tumor to this. However, when exploring suicides only, we did not find an increased risk in this group of patients.

The Nordic countries are known for their high-quality cancer registries, the overall childhood cancer incidence is comparable, and the cancer treatments are highly unified (22). The quality of data originates partly in the civil registration system, which is based on personal identity codes and multiple population-based registries, which make record linkage possible. Nationwide coverage of these unique registries and prospective data collection ensure reliable identification of all cohort members and complete follow-up. When exploring risky health behavior related deaths among cancer patients compared to comparisons, we did not find a statistically significant difference between Denmark, Finland and Sweden, which supports our approach to study these three countries as one large Nordic population.

As childhood cancer and suicide are both very rare outcomes, a large cohort of patients is essential to evaluate this type of event. Strengths of our study include the three-country-wide population-based setting with all patients included, a cohort thus free of selection or participation bias. To our knowledge, this is the largest cohort study to date to be evaluated for these outcomes. Furthermore, the registry-based design allows virtually complete follow-up and outcome ascertainment due to high quality cause of death registry data (22).

According to a recent report by the United Nations, Nordic populations have been ranked the happiest worldwide (35). On the other hand, in the Nordic countries Denmark and Finland have been in the lead of statistics for suicides from the 1960s to the beginning of the 1990s. Suicide rates have had a decreasing trend in Western Europe lately, which has raised the former Soviet countries to lead these statistics in Europe (36). There is wide variation in suicide rates globally. Based on the WHO statistics in 2016, the Nordic countries seem to exceed the global average of 10.6 suicides per 100,000 with 14.5 suicides per 100,000 in Denmark, Finland and Sweden combined. For comparison, suicide rates were 15.3 per 100,000 in the USA, 7.4 in the continent of Africa, 9.8 in the continent of America and 10.2 in the Western Pacific. (37) Due to differences in societies, health care systems and registration of suicides, our results should be generalized with caution beyond the Nordic countries.

There is a contradiction between being the happiest and the most miserable at the same time, which might indicate that happiness is not evenly distributed in the population. In our study, we noticed that cancer diagnosed in childhood has a psychological impact on the survivor as late as many years after cancer diagnosis, which might result in vulnerability to die of risky health behavior related causes.

Our results support earlier findings concerning the psychosocial well-being of childhood cancer patients. Although most patients do not resort to suicide or die of risky health behavior, a small fraction of patients appears to have excess mortality from suicide and violent, accidental, alcohol and drug-related deaths, with CNS tumor patients being a particularly vulnerable subgroup. These findings stress that psychosocial screening and support should be included in the long-term follow-up care of childhood cancer patients.

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Table 1: Basic characteristics of cancer patients

Characteristics	All cancer patients		Denmark
	n (%)	1000 pyrs	n (%)
Total	29285 (100)	358	8133 (100)
Sex			
Male	15966 (55)	188	4619 (57)
Female	13319 (45)	170	3514 (43)
Diagnostic period			
1971-1979	6325 (22)	102	1816 (22)
1980-1989	7307 (25)	122	2031 (25)
1990-1999	8202 (28)	98	2203 (27)
2000-2009	7451 (25)	36	2083 (26)
Patient's age at diagnosis			
0 - 4 years	9341 (32)	113	2532 (31)
5 - 9 years	5327 (18)	64	1512 (19)
10 - 14 years	5694 (19)	70	1554 (19)
15 - 19 years	8923 (31)	111	2535 (31)
Cancer sites			
Leukemia	7409 (25)	75	2012 (25)
Lymphoma	3958 (14)	52	1042 (13)
Central nervous system tumors	6616 (23)	80	1972 (24)
Neuroblastoma and other peripheral cell tumors	1415 (5)	14	372 (5)
Retinoblastoma	482 (2)	10	159 (2)
Renal tumors	1202 (4)	18	310 (4)
Hepatic tumors	277 (1)	2	75 (1)
Malignant bone tumors	1426 (5)	14	401 (5)
Soft tissue sarcomas	1741 (6)	21	465 (6)
Germ-cell, trophoblastic and other gonadal neoplasms	1774 (6)	25	597 (7)
Other malignant epithelial neoplasms	2596 (9)	43	619 (8)
Other and unspecified malignant neoplasms	389 (1)	4	109 (1)

Finland n (%)	Sweden n (%)
8098 (100)	13054 (100)
4345 (54)	7002 (54)
3753 (46)	6052 (46)
1712 (21)	2797 (21)
1949 (24)	3327 (25)
2241 (28)	3758 (29)
2196 (27)	3172 (24)
2656 (33)	4153 (32)
1403 (17)	2412 (18)
1556 (19)	2584 (20)
2483 (31)	3905 (30)
2196 (27)	3201 (25)
1178 (15)	1738 (13)
1720 (21)	2924 (22)
369 (5)	674 (5)
132 (2)	191 (1)
350 (4)	542 (4)
81 (1)	121 (1)
375 (5)	650 (5)
484 (6)	792 (6)
404 (5)	773 (6)
747 (9)	1230 (9)
62 (1)	218 (2)

Table 2: Characteristics and rate ratios (RR) with 95 % confidence interval (CI) of cancer patients dying

	Number of deaths related to risky health behavior		Adjusted RR (95 % CI) †
	Cancer patients	Comparison subjects	
Total	163	1134	1.25 (1.06 - 1.47)
Sex (*p* =0.98; *p* =0.47 *)			
Male	125	894	1.25 (1.04 - 1.51)
Female	38	240	1.23 (0.87 - 1.73)
Country (*p* =0.92; *p* =0.42 *)			
Denmark	42	305	1.25 (0.90 - 1.73)
Finland	63	473	1.19 (0.92 - 1.56)
Sweden	58	356	1.31 (0.99 - 1.73)
Age at patient's diagnosis (*p* =0.51; *p* =0.50 *)			
0 - 4 years	27	226	1.06 (0.71 - 1.58)
5 - 9 years	28	177	1.50 (1.01 - 2.24)
10 - 14 years	31	243	1.06 (0.73 - 1.55)
15 - 19 years	77	488	1.31 (1.03 - 1.67)
Cancer site (*p* =0.18; *p* =0.62 *)			
Leukemia	17	266 ‡	0.78 (0.48 - 1.29)
Lymphoma	30	175 ‡	1.33 (0.90 - 1.97)
Central Nervous System	44	256 ‡	1.49 (1.08 - 2.05)
Other	72	437 ‡	1.25 (0.98 - 1.61)
Time period of the diagnosis (*p* =0.96; *p* =0.40 *)			
1971 - 1979	61	567	1.20 (0.92 - 1.57)
1980 - 1989	59	361	1.26 (0.96 - 1.66)
1990 - 1999	32	163	1.24 (0.85 - 1.81)
2000 - 2009	11	43	1.48 (0.76 - 2.87)
Follow-up time from diagnosis (*p* =0.42; *p* =0.57 *)			
< 1 years	14	45	1.72 (0.94 - 3.14)
1 - 4 years	27	150	1.26 (0.83 - 1.89)
≥ 5 years	122	939	1.19 (0.99 - 1.44)
Attained age (*p* =0.84; *p* =0.99 *)			
< 10 years	12	67	1.30 (0.70 - 2.40)
10 - 19 years	31	202	1.16 (0.80 - 1.70)
20 - 29 years	62	428	1.17 (0.89 - 1.53)
30 - 39 years	40	262	1.50 (1.07 - 2.09)
≥ 40 years	18	175	1.18 (0.72 - 1.92)

†Adjusted for country, sex, attained age and diagnostic period.

‡ Comparison subjects were assigned into the same cancer stratum as their index patient.

* Likelyhood Ratio Test for RR heterogeneity. *P* -values for risky health behavior related deaths and suici

of risky health behavior related causes compared with cancer-free comparison subjects

Number of suicides		Adjusted RR (95 % CI) †
Cancer patients	Comparison subjects	
53	337	1.37 (1.02 - 1.83)
39	271	1.30 (0.93 - 1.82)
14	66	1.61 (0.91 - 2.88)
13	61	2.05 (1.12 - 3.74)
21	161	1.18 (0.74 - 1.86)
19	115	1.32 (0.81 - 2.14)
8	54	1.43 (0.68 - 3.02)
5	46	1.10 (0.44 - 2.79)
10	87	0.97 (0.50 - 1.86)
30	150	1.61 (1.09 - 2.39)
5	77 ‡	0.84 (0.34 - 2.08)
11	58 ‡	1.43 (0.75 - 2.74)
9	65 ‡	1.22 (0.60 - 2.45)
28	137 ‡	1.56 (1.04 - 2.34)
22	164	1.56 (1.00 - 2.43)
14	104	1.04 (0.60 - 1.82)
15	53	1.79 (1.01 - 3.18)
2	16	0.72 (0.17 - 3.14)
2	2	5.34 (0.75 - 37.95)
7	34	1.33 (0.59 - 3.01)
44	301	1.33 (0.97 - 1.83)
0	0	-
7	43	1.18 (0.53 - 2.64)
25	151	1.31 (0.86 - 2.00)
15	95	1.56 (0.90 - 2.69)
6	48	1.45 (0.62 - 3.39)

des, respectively.