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Geographic variation in 5-year mortality following HIV diagnosis: implications for clinical interventions

Ingrid V. Bassett[1,2,8,9,§], **Joyce Yan**[7], **Janet Giddy**[3], **Douglas Ross**[4], **Laura M. Bogart**[5], **Ashley Stuckwisch**[2], **Dani Zionts**[2], **Ravi Naidoo**[6], **Robert A. Parker**[7,8,9]

[1]Massachusetts General Hospital, Division of Infectious Diseases, Boston, Massachusetts, United States of America

[2]Massachusetts General Hospital, Medical Practice Evaluation Center, Boston, Massachusetts, United States of America

[3]McCord Hospital, Durban, South Africa

[4]St. Mary's Hospital, Mariannhill, Durban, South Africa*

[5]RAND Corporation, Santa Monica, California, United States of America

[6]Statistics South Africa, KwaZulu-Natal Provincial Office, Durban, South Africa

[7]Massachusetts General Hospital, Biostatistics Center, Boston, Massachusetts, United States of America

[8]Harvard University, Center for AIDS Research (CFAR), Boston, Massachusetts, United States of America

[9]Harvard Medical School, Boston, Massachusetts, United States of America

Abstract

Characterizing spatial distribution of HIV outcomes is vital for targeting interventions to areas most at risk. We performed spatial analysis to identify geographic clusters and factors associated with mortality in KwaZulu-Natal, South Africa. We utilized Sizanani trial (NCT01188941) data, which enrolled participants August 2010-January 2013 and obtained vital status at 5.8 (IQR 5.0–6.4) years of follow-up. We mapped geocoded addresses to 2011 Census-defined small area layer (SAL) centroids, used Kulldorff's spatial scan statistic to identify mortality clusters, and compared socio-demographic factors for SALs in and not in mortality clusters. We assigned 1,143 participants living with HIV (260 [23%] of whom died during follow-up) to 677 SALs. One lower mortality cluster (n=90, RR=0.23, p=0.022) was identified near a hospital outside Durban. SALs in the cluster were younger (24y vs 25y, p<0.001), had fewer bedrooms/household (3 vs 4, p<0.001), had more females (52% vs 51%, p=0.013) and residents with no schooling past age 20 (4% vs 3%, p<0.001) or no education at all (4% vs 3%, p<0.001), and had fewer residents with

[§]Corresponding author: Ingrid V. Bassett, MD, MPH, 100 Cambridge Street, 16th Floor, Boston, MA 02114, USA, ibassett@mgh.harvard.edu, Tel: +1 617 726 0637, Fax: +1 617 726 4120.
*Current affiliation: Blessed Gérard's Care Centre, Mandeni, South Africa

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The authors declare that they have no competing interests.

income >3,200 ZAR/month (5% vs 9%, p<0.001). SALs in the cluster also had reduced access to piped water (p<0.001), refuse disposal (p<0.001), and toilets (p<0.001). Targeted interventions may improve outcomes in areas with similar characteristics.

Keywords

HIV/AIDS; South Africa; mortality; geographical information systems

Introduction

South Africa has the highest HIV prevalence globally, with 7.8 million people living with HIV (PLWH) and 230,000 new infections in 2020 (UNAIDS, 2020). The scale-up of antiretroviral therapy (ART) has increased the life expectancy of PLWH; yet, HIV/AIDS remains a leading cause of death, with 83,000 deaths in 2020 (Pillay-van Wyk et al., 2016; UNAIDS, 2020). Mortality rates are exceptionally high in KwaZulu-Natal, where we and others have previously shown that mortality risk is associated with contextual factors such as mental health, social support, self-perceived barriers to care, and competing needs (Bassett et al., 2017, 2019; Pillay-van Wyk et al., 2016). Further characterization of geographical risk factors is needed to understand mortality outcomes fully.

Geographic Information Systems can map disease distributions, associated risk factors, and prevention and treatment services (Boyda et al., 2019). Many studies have used spatial clustering (i.e., classifying spatial objects based on specific characteristics, where objects in a cluster are like each other and unlike non-cluster objects) to understand HIV prevalence in sub-Saharan Africa. These studies have found HIV to be distributed in localized clusters and to be heterogeneous between provinces, districts, and finer scales (Holmes et al., 2020; Meyer-Rath et al., 2018; Tanser et al., 2018; Wabiri et al., 2016; Waruru et al., 2018). HIV prevalence and mortality in rural South Africa are concentrated in peri-urban regions, around major towns, roads, and commercial activity, indicating that urbanization may play a prominent role in cluster locations (Meyer-Rath et al., 2018; Namosha et al., 2013; Tanser et al., 2018; Tlou et al., 2017a, 2017b). Other socio-economic, mobility, and geographic factors may also influence clustering (Bulstra et al., 2020; Muttai et al., 2021; Wabiri et al., 2016).

Identifying areas with excess HIV mortality is essential to direct public health interventions appropriately. Geospatial analyses have allowed for microtargeting of prevention services based on risk, leading to declining HIV incidence and increasing equity of the HIV response (Holmes et al., 2020). Further, the United States President's Emergency Plan for AIDS Relief, the Global Fund, and the Joint United Nations Programme on HIV/AIDS endorse focusing resources on higher-burden geographical areas and facilities (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2014; The Global Fund, 2016; U.S. President's Emergency Plan for AIDS Relief, 2022). With declining program funds and increased access to HIV services, geospatial analysis is increasingly vital for targeting service delivery to finer geographic units.

In this analysis, we used spatial statistical analysis to identify geographic clusters and area-level demographic and socio-economic factors associated with mortality in an urban South African setting with high underlying HIV prevalence and mortality.

Materials and methods

Study setting and design

The study occurred in KwaZulu-Natal, a southeast province of South Africa that is 94,361 km^2 and has 11,531,628 people, making it the second-most populous province in South Africa (South African Government, n.d.). The study population was concentrated around eThekwini, an urban metropolitan municipality that contains the coastal city of Durban. eThekwini has 3,702,231 people and includes urban, peri-urban, and rural areas (Govere et al., 2021).

The analysis includes data from the Sizanani Trial (NCT01188941). This randomized controlled trial examined the efficacy of health system navigation and short messaging service reminders on linkage to and retention in HIV/TB care. From August 2010-January 2013, we enrolled adults (≥18 years) with unknown HIV status presenting for HIV testing at two hospital outpatient departments at McCord (urban) and St. Mary's (peri-urban) Hospitals and two nurse-driven municipal primary health clinics (Tshelimnyama and Marianridge Clinics) within the service area of St. Mary's Hospital. Study enrollment, consisting of informed consent and a baseline questionnaire, occurred before HIV testing. This trial is described elsewhere (Bassett et al., 2013, 2016, 2017). Since there was no significant difference between linkage to HIV care, TB treatment completion, or one-year mortality between study arms, we pooled data from the PLWH in intervention and control groups into a single cohort in the current study.

The McCord Hospital Medical Research Ethics Committee, St. Mary's Hospital Research Ethics Committee, University of KwaZulu-Natal Biomedical Research Ethics Committee, and Mass General Brigham Institutional Review Board (Protocol 2011-P-001195, Boston, MA) approved this study.

Data elements

Residential addresses were collected at enrollment for each Sizanani trial participant and were manually geocoded by AfriGIS, a Pretoria-based technology company. We then mapped the geocoded coordinates into small area layer (SAL) spatial units defined by 2011 South African Census data (Statistics South Africa, 2011). The SAL unit comprises aggregated enumeration areas (i.e., the work area for an individual Census enumerator) at a finer scale than sub-place (i.e., named villages, suburbs, etc.) data. All individual coordinates falling within a SAL were remapped to the centroid of that SAL and characterized by SAL data. SAL-level characteristics included: median age; the median number of bedrooms per household; race, gender, education, income, and employment percentages; primary household type; main cooking, heating, and lighting methods; and availability of piped water, refuse disposal, and toilets.

The primary outcome variable for this study was mortality. We elicited five-year all-cause mortality events from the South Africa National Population Register, estimated to incorporate at least 90% of deaths nationwide (Cornell et al., 2014; Johnson et al., 2015). We used South African ID numbers obtained at enrollment to match participants to the National Population Register in November 2017; the median follow-up was 5.8 years (IQR 5.0–6.4 years).

Analysis

We used Kulldorff's purely spatial scan statistic in SaTScan version 9.7 (https://www.satscan.org/) to detect spatial clusters of high or low mortality. As the outcome of interest was a binomial variable (alive or dead at five years), we used the Bernoulli model for scanning. The SaTScan software uses a circular window that moves across space, noting the number of observed and expected observations inside the window at each location and adjusting for heterogeneous population density and distribution. The likelihood function is maximized over all window locations and sizes, and the window with the maximum likelihood constitutes the cluster that is least likely to have occurred by chance. The p-value is obtained by comparing the rank of the maximum likelihood from the actual data set with the maximum likelihoods from 999 Monte Carlo replications of the data set generated under the null hypothesis of no clusters. We performed the Kulldorff spatial cluster detection over the 677 SAL centroid locations included in this analysis, using a maximum spatial cluster size of 25% of the population and a minimum of 2 cases per cluster for high mortality to define clusters. Clusters with a relative risk >1.0 at a p-value <0.05 were considered significant clusters of higher mortality, while those with a relative risk <1.0 and a p-value <0.05 were deemed significant clusters of lower mortality. For significant clusters, we report the number of observed and expected cases, relative risk, and p-values.

Once clusters were identified, we used the 2011 Census SAL characteristics data to compare geographic areas where mortality clusters (high or low) were present to areas without clusters. For continuous variables (e.g., age; the number of bedrooms; percentages of race, gender, education, income, and employment), we used Wilcoxon Rank Sum tests to compare population-weighted averages for SALs in and not in the clusters. We used chi-square tests for categorical variables (e.g., primary household type; main cooking, heating, and lighting methods) and we conducted Cochran-Armitage trend tests for ordered categorical variables (e.g., availability of piped water, refuse disposal, and toilets). We report results as medians and interquartile ranges or counts and percentages and provide p-values.

Results

Spatial clusters of mortality

We analyzed data from 1,143 PLWH, of whom 260 (23%) died during the follow-up period. We assigned these 1,143 PLWH to 677 SAL centroids throughout KwaZulu-Natal. One significant cluster (n=90) of lower mortality was identified, with only five mortality events observed, although 20.5 events would be expected, with a cluster relative risk of 0.23 (p=0.022) (Figure 1). The cluster was located near the St. Mary's Hospital, Tshelimnyama Clinic, and Marianridge Clinic enrollment sites in a peri-urban area of eThekwini. We identified no significant clusters of higher mortality; the smallest p-value for a higher mortality cluster was 0.22.

Characteristics of the lower mortality cluster

SALs in the cluster were on average younger (24y vs. 25y, p<0.001), had fewer bedrooms per household (3 vs. 4, p<0.001), had higher proportions of females (52% vs. 51%, p=0.013) and residents with no schooling past age 20 (4% vs. 3%, p<0.001) or no education at all (4% vs. 3%, p<0.001), and had lower proportions of residents with monthly income >3,200 ZAR (5% vs. 9%, p<0.001) (Table 1). Additionally, there was a small but statistically significant difference in the proportion of Black African race, with a slightly lower proportion among SALs in the cluster (99.2% vs. 99.4%, p=0.007). Employment did not differ between the cluster and non-cluster areas.

100% of the SALs in the cluster had formal (e.g., houses, flats, apartments, or townhouses) instead of informal or traditional households as the primary household type and electricity as the main cooking, heating, and lighting method. These factors were not significantly different between the cluster and non-cluster areas.

SALs both in and not in the cluster most often accessed piped water inside a dwelling; however, the cluster tended towards piped water that was further away from households (p<0.001), with a higher proportion accessing piped water from a nearby community stand. Refuse was often removed by a local authority or private company at least once a week, both in and not in the cluster; however, SALs in the cluster tended towards less refuse disposal (p<0.001), with a higher proportion maintaining their own refuse dump. The most common toilet was a flush toilet connected to a sewage system both in and not in the cluster; however, the cluster tended toward lower quality toilets (p<0.001), with a higher proportion of chemical, pit, and bucket toilets.

Discussion

This study found a single cluster of lower 5-year all-cause mortality among PLWH in the Sizanani trial, in a peri-urban area near Durban, despite socio-demographic risk factors including lower education, income, and poorer access to water, refuse disposal, and toilets. The cluster was in the catchment area of St. Mary’s Hospital, a district hospital enrollment site serving a relatively poor population approximately 20 kilometers west of Durban. The municipal clinic enrollment sites, Tshelimnyama and Marianridge, also referred to St. Mary’s for ART initiation after HIV testing. The area is semi-rural, surrounded by townships and informal settlements.

The lower mortality cluster near the peri-urban study enrollment sites indicates that people who tested for HIV near their residence experienced more favorable health outcomes in this study. We have previously found pre-treatment losses to care to be more likely among people that lived ≥10 kilometers from the McCord or St. Mary’s testing centers (Losina et al., 2010). Further, people who lived ≥5 kilometers from the test sites had higher odds of late-stage HIV disease presentation, which is associated with higher mortality (Drain et al., 2013). Thus, participants in the cluster near the peri-urban testing sites may have received more timely HIV care, resulting in lower mortality.

We also found the residential addresses for Sizanani participants to be distributed across KwaZulu-Natal, indicating that some participants traveled further than their closest clinic to access HIV testing. Studies have commonly found that PLWH travel to more distant clinics to avoid the stigma of being recognized by community members or because they perceive remote clinics to provide higher quality HIV care (Akullian et al., 2016; Bassett et al., 2015; Mee et al., 2020). However, the logistical challenges of getting to a faraway clinic can limit ongoing care receipt, such that increased ART uptake and decreased mortality risk are associated with a shorter distance to the clinic (Cooke et al., 2010; Hannaford et al., 2021; Hendrickson et al., 2018; Sartorius, 2013). Differentiated HIV treatment models may improve outcomes by tailoring care to individual patients, potentially reducing stigma and the distance traveled to access care (Boyda et al., 2019; Ehrenkranz et al., 2019; Grimsrud et al., 2017; Sharer et al., 2019).

We did not observe a lower mortality cluster near the urban enrolment site (McCord Hospital), potentially reflecting differences between the McCord and St. Mary's Hospital areas. St. Mary's Hospital received higher state subsidies during the study period, allowing them to charge lower fees than McCord. Further, the approximately 20 alternative accredited ART initiation centers in greater Durban were concentrated around McCord, allowing more anonymity in HIV testing and care initiation. However, a higher number of alternative locations may have contributed to a higher loss to care rate, as there may inherently be less community or healthcare support among clinic populations that are not as clearly defined (Losina et al., 2010).

Conversely, St. Mary's Hospital had an accompanying church, children's school, and monastery and conducted extensive community outreach to other clinics and individuals in their catchment area through efforts such as community health messaging and involvement of community health workers. These community services and connections may have encouraged increased healthcare engagement and positive health benefits among patients living in the area. We have also found that receiving HIV testing at McCord versus St. Mary's was correlated with poorer social support (Drain et al., 2015). Targeted expansion of interventions such as support groups or adherence clubs may improve outcomes in similarly urban areas as social support is a major facilitator of linkage and adherence to HIV care (Croome et al., 2017; Fox et al., 2019; Kave et al., 2019).

Prior geospatial studies of mortality in South Africa have focused on rural areas. In contrast to our research, they have identified peri-urban regions as higher risk, primarily due to high underlying HIV prevalence relative to the study area (Namosha et al., 2013; Tlou et al., 2017a, 2017b). Our lower mortality cluster was characterized by traits typical of a poorer, more rural area, with smaller households and relatively low education, income, and sanitation. However, numerous other studies have shown lower socio-economic status as a significant mortality risk factor among PLWH (Probst et al., 2016; Sartorius, 2013; Sartorius et al., 2010; Sartorius & Sartorius, 2013). Further, improved access to water and sanitation significantly reduces diarrheal deaths due to inadequate water, sanitation, and hygiene (World Health Organization, n.d.). Therefore, it is likely that community services, cohesion, social support, or other factors contributed more to the lower mortality than our observed socio-demographic trends. South Africa should continue efforts toward income equality and access to education, piped water, and sanitation; still, our study indicates that health services targeting relatively poor areas can also encourage positive health outcomes (Mayosi et al., 2012).

Our study has several limitations. The first is that we recruited participants in and around Durban, so findings may not be generalizable to the entirety of KwaZulu-Natal, particularly more rural areas. Second, since we relied on area-level characteristics obtained from the Census data, we did not include individual contextual factors that may have contributed to our observed outcomes. Finally, we could not determine the cause of our participants' deaths, so we cannot confirm that they were HIV-related; however, data suggest that HIV/AIDS-related deaths drove mortality in South Africa during the study period (Pillay-van Wyk et al., 2016).

In conclusion, we found a lower mortality area in KwaZulu-Natal to be younger, with smaller households, with more females and residents with limited/no schooling, and fewer residents in the high-income category or with optimal access to sanitation (water, refuse, toilets). A local district hospital providing tailored outreach, HIV testing, community-related interventions, and ongoing care may have mitigated these socio-demographic risk factors. Targeted interventions that improve access to and acceptability of HIV care may reduce deaths among PLWH in similar peri-urban areas with high HIV prevalence. Adherence clubs, decentralized medication delivery in community venues (e.g, schools, churches), and self-forming client-managed groups can improve retention in care and long-term virologic suppression, while leveraging community strengths (Fox et al., 2019, Fatti et al., 2021, Jobarteh et al., 2016).

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Data availability statement

The data supporting this study's findings are available from the corresponding author (IVB) upon reasonable request.

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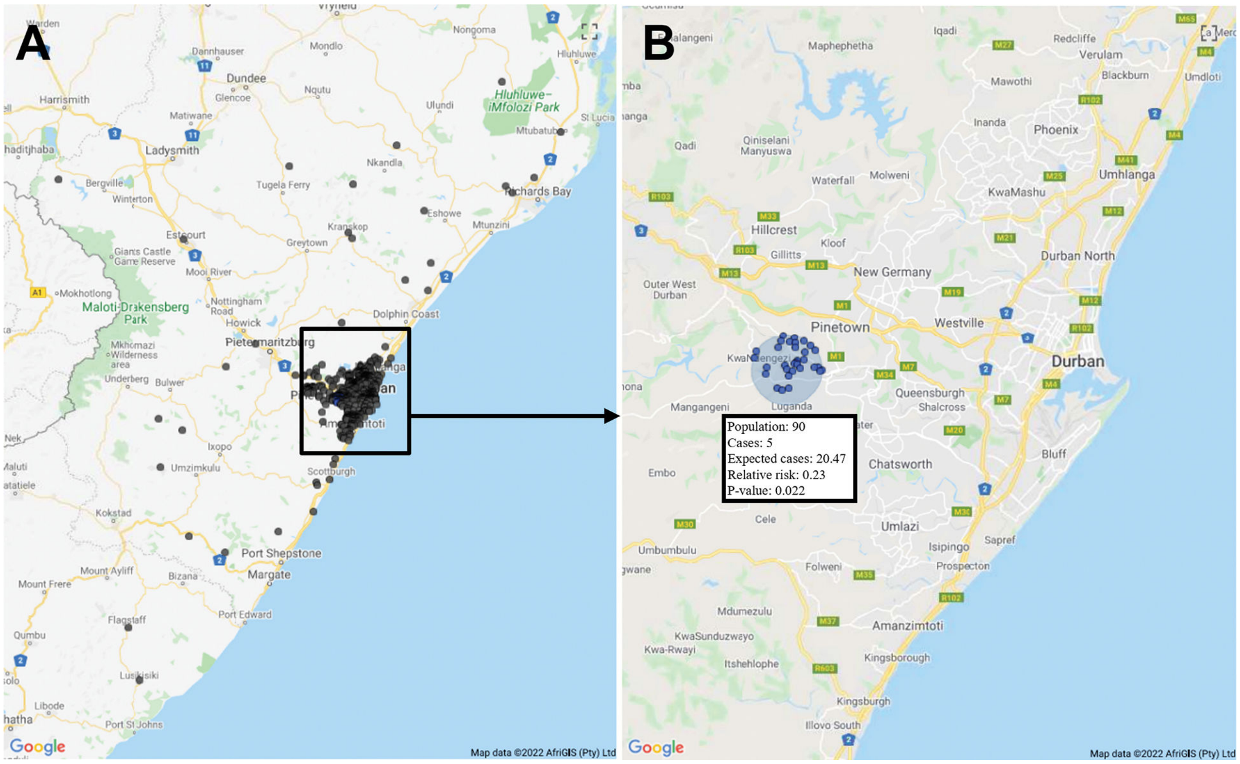

Figure 1.

Spatial cluster of lower mortality. (A) Distribution of small area layer centroids of study participants throughout KwaZuluNatal. (B) Lower mortality cluster in relation to the greater Durban area.

Table 1.

Small Area Layer Characteristics

Characteristics, median [IQR] or n (%)	In Low Mortality Cluster (n = 90)	Not In Low Mortality Cluster (n = 1053)	p-value
Age, years	24.0 [23.0–25.0]	25.0 [23.0–27.0]	<0.001
Median bedrooms per household	3.0 [2.0–4.0]	4.0 [2.0–5.0]	<0.001
Percent Black African	99.2 [66.8–99.5]	99.4 [86.7–99.8]	0.007
Percent female	52.0 [50.8–53.2]	51.4 [49.5–53.1]	0.013
Percent no school past age 20	4.0 [3.0–7.0]	3.0 [1.0–5.0]	<0.001
Percent no school at all	4.0 [3.0–7.0]	3.0 [1.0–5.0]	<0.001
Percent earning >3,200 ZAR/month	5.1 [3.5–6.9]	9.2 [5.3–18.7]	<0.001
Percent employed	38.7 [31.3–45.3]	41.0 [30.3–51.1]	0.143
Main household type			
Formal	90 (100.0)	967/1046 (92.5)	0.063
Informal	0 (0.0)	40/1046 (3.8)	
Traditional	0 (0.0)	37/1046 (3.5)	
Other	0 (0.0)	2/1046 (0.2)	
Main cooking method			
Electricity	90 (100.0)	1012/1046 (96.8)	0.221
Wood	0 (0.0)	25/1046 (2.4)	
Paraffin	0 (0.0)	9/1046 (0.9)	
Main heating method			
Electricity	90 (100.0)	995/1046 (95.1)	0.332
Wood	0 (0.0)	40/1046 (3.8)	
Paraffin	0 (0.0)	7/1046 (0.7)	
Coal	0 (0.0)	2/1046 (0.2)	
Gas	0 (0.0)	2/1046 (0.2)	
Main lighting method			
Electricity	90 (100.0)	1008/1046 (96.4)	0.184
Candles	0 (0.0)	37/1046 (3.5)	
Paraffin	0 (0.0)	1/1046 (0.1)	
Piped water			
Piped (tap) water inside dwelling/institution	43 (47.8)	712/1051 (67.8)	<0.001
Piped (tap) water inside yard	16 (17.8)	256/1051 (24.4)	
Piped (tap) water on community stand: distance less than 200m from dwelling/institution	30 (33.3)	52/1051 (5)	
Piped (tap) water on community stand: distance between 200m and 500m from dwelling/institution	1 (1.1)	14/1051 (1.3)	
Piped (tap) water on community stand: distance greater than 1000m (1km) from dwelling/institution	0 (0.0)	6/1051 (0.6)	
No access to piped (tap) water	0 (0.0)	11/1051 (1.1)	
Refuse			
Removed by local authority/private company at least once a week	66 (73.3)	921/1046 (88.1)	0.005

Characteristics, median [IQR] or n (%)	**In Low Mortality Cluster (n = 90)**	**Not In Low Mortality Cluster (n = 1053)**	**p-value**
Removed by local authority/private company less often	4 (4.4)	5/1046 (0.5)	
Own refuse dump	20 (22.2)	106/1046 (10.1)	
Communal refuse dump	0 (0.0)	2/1046 (0.2)	
No rubbish disposal/Other	0 (0.0)	12/1046 (1.1)	
Toilet			
Flush toilet (sewage system)	41 (45.6)	783/1046 (74.9)	<0.001
Flush toilet (septic tank)	8 (8.9)	57/1046 (5.5)	
Chemical toilet	24 (26.7)	59/1046 (5.6)	
Pit toilet with ventilation	3 (3.3)	67/1046 (6.4)	
Pit toilet without ventilation	11 (12.2)	51/1046 (4.9)	
Bucket toilet/None/Other	3 (3.3)	29/1046 (2.8)	