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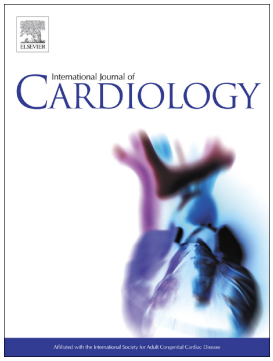

Prevalence and profile of "seasonal frequent flyers" with chronic heart disease: Analysis of 1598 patients and 4588 patient-years follow-up

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Prevalence and profile of "seasonal frequent flyers" with chronic heart disease: Analysis of 1598 patients and 4588 patient-years follow-up

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Abstract

Background: Peaks and troughs in cardiovascular events correlated with seasonal change is well established from an epidemiological perspective but not a clinical one.

Methods: Retrospective analysis of the recruitment, baseline characteristics and outcomes during minimum 12-month exposure to all four seasons in 1,598 disease-management trial patients hospitalised with chronic heart disease. Seasonality was prospectively defined as ≥4 hospitalisations (all-cause) AND >45% of related bed-days occurring in any one season during median 988 (IQR 653, 1,394) days follow-up.

Results: Patients (39% female) were aged 70±12 years and had a combination of coronary artery disease (58%), heart failure (54%), atrial fibrillation (50%) and multimorbidity. Overall, 29.9% of patients displayed a pattern of seasonality. Independent correlates of seasonality were female gender (adjusted OR 1.27, 95% CI 1.01 - 1.61; p=0.042), mild cognitive impairment (adjusted OR 1.51, 95% CI 1.16 - 1.97; p=0.002), greater multimorbidity (OR 1.20, 95% CI 1.15 - 1.26 per Charlson Comorbidity Index Score; p<0.001), higher systolic (OR 1.01, 95%CI 1.00 - 1.01 per 1 mmHg; p=0.002) and lower diastolic (OR 0.99, 95% CI 0.98 - 1.00 per 1 mmHg; p=0.002) blood pressure. These patients were more than two-fold more likely to die (adjusted HR 2.16, 95% CI 1.60 – 2.90; p<0.001) with the highest and lowest number of deaths occurring during spring (31.7%) and summer (19.9%), respectively.

Conclusions: Despite high quality care and regardless of their diagnosis, we identified a significant proportion of "seasonal frequent flyers" with concurrent poor survival in this real-world cohort of patients with chronic heart disease.

Key words

Cardiovascular Seasonality • cardiovascular disease • heart failure • atrial fibrillation • coronary artery disease

Abbreviations

AF	Atrial fibrillation
CAD	Coronary artery disease
CVD	Cardiovascular disease
HF	Heart failure
KGCCS	Köppen-Geiger Climate Classification System

1.1 Introduction

Despite gains in reducing premature mortality, the burden of cardiovascular disease (CVD) remains substantial; by 2035 it is estimated that >130 million adults (45.1%) in the United States will have developed CVD at an annual cost of ~$US750 billion in health care expenditure [1]. Much of this burden is due to a combination of coronary artery disease (CAD), atrial fibrillation (AF), requiring long-term management in the community and episodic hospital admissions during periods of clinical instability [2] [3]. An important but often overlooked contributor to the growing burden of CVD worldwide is the phenomenon of "seasonality" characteristed by annual peaks and troughs in cardiovascular event rates coinciding with seasonal changes in climatic conditions and acute weather events [4–7]. Typically, seasonality results in a 10-20% variation in hospitalisation (both de novo and recurrent) and mortality rates throughout the year; the annual problem of "hospital bed-block" and "ambulance ramping" during the winter months, as well as random spikes in mortality during extreme heat-waves or cold-snaps, being the most recognisable manifestation of this phenomenon [6]. However, there has been relatively little focus on this phenomenon from a clinical perspective [6].

2.1 Study Aims & Hypothesis

We hypothesise that a natural starting point of any investigation of seasonality from a cardiovascular perspective is predominantly older patients with chronic forms of heart disease and multimorbidity. [6] This is for two principal reasons – 1) it is within this growing patient population that rates of recurrent hospitalisation and potentially preventable mortality are highest, with a significant component of recurrent "frequent flyers" to hospital the main focus of hospital avoidance programs; AND 2) if, as we've hypothesised [6], that

seasonality is largely driven by a complex interaction between physiology, clinical profile, environment and behaviours, it is within this patient population that we are most likely to identify such an interaction.

Our specific aim, therefore, was to retrospectively examine the prevalence and characteristics of seasonality in a large, real-world cohort of patients hospitalised with a combination of CAD, CHF and/or AF followed-up for at least 12 months. Apart from ensuring all patients were exposed to all four seasons during follow-up, this cohort had been subject to comprehensive profiling to facilitate identification of potential bio-behavioural correlates of any observed seasonality. Moreover, in selecting patients subject to high-levels of care, we had the opportunity to determine if seasonality explains, at least partially, why some patients appear to be "resistant" to otherwise proven models of care designed to reduce morbidity and mortality [8–10].

3.1 Methods

Consistent with a previous report examining composite health outcomes across three disease management trials [11], we conducted a retrospective analysis of the timing of recruitment, baseline characteristics and health outcomes of patients admitted to hospital with chronic heart disease (n=2026) who participated in one of four disease management trials. Details of the design of each pragmatic disease management trial (all four trials conformed to the ethical guidelines of the 1975 Declaration of Helsinki and were prospectively registered via www.anzctr.org.au), rationale and individual trial outcomes reported according to CONSORT guidelines for pragmatic trials of health service interventions [12, 13], have been published previously [14–17].

3.1.1 Study cohort

This composite study cohort comprises patients enrolled in a series of disease management trials undertaken by our group with the following key features: 1) chronic heart disease (most presented with acute coronary syndrome/CAD), but not HF (n=624), enrolled in the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) Study [14]; 2) chronic AF, but not HF (n=335), enrolled in the Standard versus Atrial Fibrillation spEcific managemenT StrategY (SAFETY) Trial [15]; and 3) chronic HF with multimorbidity enrolled in the Which Heart failure Intervention is most Cost-effective & consumer friendly in reducing heart failure Hospital care (WHICH?) Trial (n=280) [16]; and 4) the subsequent Which Heart failure Intervention is most Cost-effective in reducing Hospital stay (WHICH? II) Trial (n=787) [17].

3.1.2 Study eligibility

All 2,026 patients who underwent standardized profiling (during their index admission) and study follow-up (post-randomization) as part of these trials were eligible for inclusion. However, in order to identify and characterize underlying seasonality both at the point of study recruitment and during stuy follow-up, we applied two key inclusion criteria: 1) recruited during a full 12-month calendar (January to December) period for that study and 2) subject to a minimum 12 months follow-up and, subsequent, exposure to all four seasons/climatic conditions. Overall, 1598 patients (from NIL-CHF (n=503 31.5%), SAFETY (n= 281, 17.6%), WHICH? I (n= 211, 13.2%) and WHICH? II (n = 603, 37.7%) trial cohorts fulfilled these criteria.

3.1.3 Study sites

With the exception of the single-centre NIL-CHF Study, study patients were recruited from tertiary hospitals across Australia subject to varying climates and acute weather conditions, but with four distinct seasons that appear critical to provoking seasonality [6]. On

this basis, patients lived in Melbourne, Victoria (main Köppen-Geiger Climate Classification – Marine West Coast Climate), Adelaide, South Australia (Mediterranean Climate), Canberra, Australian Capital Territory (Marine West Coast Climate), Sydney, New South Wales (Humid Subtropical) and Brisbane, Queensland (Humid Subtropical) [18].

3.1.4 Baseline Profile

Equivalent and highly stringent methods for comprehensive profiling of patients during their index (qualifying) admission were applied to each study cohort (see **Table 1**). This included socio-demographic status, past medical history, clinical profile, in-hospital management and post-discharge care. The primary diagnosis of all patients was determined by the treating cardiologist confirmed with documented cardiac structure and function evaluated by echocardiography (all cases) and other cardiac investigations (including coronary angiography), where appropriate.

3.1.5 *Seasonality*

Firstly, we examined potential differences in the absolute number and characteristics of trial patients according to the season in which they were recruited. This comprised the summer (December to February), autumn (March to May), winter (June to August) and spring (September to November) periods of 2008-2017. With minimal loss to follow-up, all subsequent readmissions and deaths were documented via individually linked, electronic records during a median of 988 (IQR 653, 1394) days follow-up.

There are currently no published or agreed clinical definitions of seasonality. To identify patterns of seasonality using a set of conservative parameters, therefore, we firstly categorised all events (readmission or death) during a minimum 12-month follow-up post-index hospitalisation according to the season in which it occurred. In order to minimise the possibility of random clustering of events in one particular season, we then applied a

prospectively formulated/high-threshold definition to observed patterns of hospitalisation and bed-stay: 1) minimum of four hospitalisations for any reason including their index admission; AND 2) >45% of related bed-days occurring in one season during median 988 (IQR 653, 1394) days follow-up.

3.1.6 Statistical Analyses

No formal analysis of study power was conducted. However, we hypothesised that >10% (>150 patients) would exhibit seasonality. Profiling and outcome data from the four studies were pooled and analysed using SPSS v24.0. Discrete variables are summarized by frequencies and percentages; and continuous variables by standard measures of central tendency and dispersion using means (standard deviation [SD]) and medians (interquartile range [IQR]) where appropriate. Between group comparisons were assessed using the one-way analysis of variance (ANOVA), the Mann Whitney U test, the Kruskal-Wallis test and the Chi-squared test (with calculation of odds ratios [OR] and 95% confidence intervals [CIs]), where appropriate. Survival data were used to generate Kaplan-Meier survival curves and group comparisons made with the log-rank test. A Cox Proportional Hazards Model using comprehensive baseline profiling data was constructed to identify the independent correlates of all-cause mortality using a backwards, step-wise approach (the assumption of proportional hazards being confirmed).

4.1 Results

4.1.1 Baseline characteristics

The baseline characteristics of the cohort according to the season in which their index admission occurred are summarised in **Table 1**. Overall, 118 more patients were identified and recruited in autumn/winter than spring/summer: a marked summer trough (equivalent

to 60 fewer patients when assuming an even rate of recruitment over the four seasons) in recruitment being evident. A number of potentially important differences (from a socio-economic, behavioural and clinical perspective) were evident. For example, compared to those recruited in the heat of summer, those recruited in the colder/wetter winter season were less educated (24% versus 16%), had higher risk alcohol use (16% versus 12%), a higher frequency of total cholesterol levels ≥4.0 mmol/L (50% versus 47%), higher systolic BP (135 [24] versus 132 [24] mmHg) and heart rate (86 [27] versus 84 [26] beats/min), less type 2 diabetes (33% versus 37%), more HF (57% versus 52%) and were more likely to be specifically admitted with a primary diagnosis of heart disease (77% versus 72%); $p<0.05$ for all comparisons.

4.1.2 Health outcomes during long-term follow-up

During a total of 4,558 patient-years follow-up, 1,158 patients (72.5%) accumulated 5,825 readmissions and 35,292 bed-days. Beyond minimum 12-month follow-up, 186 patients (11.6%) died.

4.1.3 Health outcomes according to season

Figure 1 shows the pattern of index and recurrent hospitalisation (6,265 admissions and 38,499 bed-days combined) and all-cause mortality according to the month (and season) in which it occurred; both overall and according to the 3 main forms of heart disease diagnosed during the index admission (HF, AF, CAD). Overall, hospital activity levels (in terms of bed-days) reached peak levels in the winter months (a differential of 2029 days equivalent to 19% more bed-days) versus trough levels in the summer months. Alternatively, peak mortality (22 more deaths equivalent to a 37% difference) occurred during spring compared to an equivalent trough in summer.

4.1.4 Seasonal Patterns

Overall, 478/1,598 patients (29.9%, 95% CI 27.7% to 32.2%) demonstrated seasonality during study follow-up. This phenomenon was evident in all four seasons, with 107 (6.7% of total cohort), 110 (6.9%), 128 (8.0%) and 117 (7.3%) of these 478 patients displaying a predominant pattern of recurrent hospital stay in summer (0.64±0.14 of all bed-days occurred in that season), autumn (0.63±0.14), winter (0.62±0.16) and spring (0.65±0.16), respectively. A further 16 patients demonstrated dual seasonality (>45% bed-stay in two different seasons) with most (12/16 patients) admitted across the winter/spring months.

On an adjusted basis, those displaying seasonality were more likely to be female (33.8% *versus* 27.4% of males - OR 1.27, 95% CI 1.01, 1.61; p=0.042), with mild cognitive impairment (32.8% *versus* 22.3% intact cognition among 918 patients – OR 1.51, 95% 1.16, 1.97; p=0.002), greater multimorbidity (mean Charlson Index of Comorbidity Score 6.7±2.6 *versus* 5.2±2.6 – OR 1.203, 95% CI 1.15, 1.26 per unit score increase; p<0.001) and higher systolic BP (137±24 *versus* 133±23 mmHg – OR 1.01, 95% CI 1.10, 1.01 per unit score increase; p=0.002) and lower diastolic BP (74±14 *versus* 76±15mmHg – OR 0.99, 95% CI 0.98, 1.00 per unit score increase; p=0.002). Importantly, neither the specific cardiac diagnosis(es) nor the type of post-discharge management modulated observed seasonality.

Table 2 summarises the pattern of seasonality evidence in the 1,158 patients (72.5%) who experienced at least one hospital readmission. Those who didn't demonsrate seasonality (59% of this sub-group) contributed to a steady baseline of 42% - 46% of hospital activity each season. By contrast, those demonstrating seasonality in the summer (9.2% of those readmitted at least once), autumn (9.5%), winter (11.1%) and spring (10.1%) contributed disproportionately to 22%-26% of admissions and 31%-37% of bed-stay in their equivalent peak seasons.

Figure 2 demonstrates that, on an adjusted basis, seasonality (along with advancing age, longer stay at index admission, a diagnosis of HF and greater comorbidity) was independently associated with a 2.2-fold increased risk of all-cause mortality; overall 103/478 (21.6%) patients displaying seasonality versus 68/680 (10.0%) of the rest died during follow-up. Moreover, the pattern of mortality according to season, was markedly different ($p<0.001$) with 13 (12.6%), 24 (23.3%), 31 (30.1%) and 35 (34.0%) of deaths among those displaying seasonality occurring in the summer, autumn, winter and spring, respectively ($p<0.001$). The equivalent distribution of deaths in the remaining cohort was more even, but also with some seasonal variations: 15 (22.0%) in autumn, 22 in spring (32.4%), 19 (27.9%) in summer and 12 (17.6%) in winter.

4.1 Discussion

The primary aim of this unique study of seasonality from a clinical perspective, was to identify and characterise seasonality within a real-world cohort of patients admitted to hospital with chronic heart disease and multimorbidity. Overall, despite intensive intervention to minimise recurrent hospitalisation and premature mortality [11, 15, 16, 19], 29.9% of patients displayed a distinctive pattern of seasonality. Moreover, seasonality was not confined to winter. As previously postulated, a combination of socio-economic, behavioural, environmental and clinical/biological factors, some of which might be amenable to modification, appear to contribute to this phenomenon [6]. Critically, although it is true our definition of seasonality mandated that individuals be "frequent flyers" in terms of recurrent hospitalisation, it is important to note that "*seasonal frequent flyers*" make-up the majority of this high-risk/high-cost group. On this basis, we have yet to identify how to define seasonality at the individual level. However, the conservative definition we applied in this study represent a good starting point. Beyond explaining high-levels of recurrent

hospitalisation despite the application of high-quality care, on an adjusted basis, those displaying seasonality had a more than two-fold risk of dying (predominantly in spring).

Despite the retrospective nature of our analyses and notwithstanding many epidemiological reports [20–23], to our knowledge, this study represents one of the few studies to address this phenomenon from a clinical perspective. Given a lack of evidence, current clinical guidelines focussing on chronic heart disease rarely address this phenomenon [24]. Whilst reinforcing that this phenomenon is typically characterized by winter peaks and summer troughs in morbid and fatal events, we found evidence of seasonal vulnerability across all four seasons. For example, peak mortality occurred in Spring. While this may highlight the arbitrary definition of each season (many deaths occurred in early Spring), it highly possible that the provocation of clinical instability during winter resulted in many individuals becoming fatally vulnerable to any further provocations of cold/climatic instability in typically variable Spring conditions. This may also reflect the unique Australian events (e.g. the deadly asthma thunderstorm in the spring of 2016 [25]).

With a predominantly warmer/milder climate, Australia potentially represents an ideal “laboratory” to study seasonality/winter peaks independent of extremely cold temperatures. [21] Accordingly, mechanisms underlying seasonal patterns of morbidity and mortality are complex and go beyond a simple, linear relationship between ambient temperature and risk of a cardiovascular event. Indeed, counterintuitively, the magnitude of seasonality at the population level appears to be greater in those populations living in milder climates [4, 26]; suggesting that this phenomenon is driven by an interaction between numerous environmental, physiological and behavioural factors at the individual level. On this basis, an individual’s vulnerability to seasonality may be dependent on their ability to adapt bio-behaviourally (i.e. their resilience) to provocative variations in climatic/environmental

conditions. Behavioural seasonality has been demonstrated in several studies [27, 28], where peaks in alcohol consumption and energy intake (including increases in fat-intake) and troughs in physical activity levels, occur in the cooler months; coinciding with winter peaks in cardiovascular events [20, 29, 30]. While excessive alcohol consumption has been directly linked to the onset of AF [31], poorer lipid profiles and increased oxidative stress, in conjunction with other "protective" mechanisms (i.e. shivering) in response to exposure to the cold, impair vascular reactivity and provoke hypertension and tachycardia with deleterious cardiac consequences [32]. These (mal)adaptations to behaviour and environment, combined with reductions in plasma volume and increases in blood viscosity [33, 34], intensify blood shear stress triggering platelet activation and inflammation [35, 36]. Alternatively, provocation of cardiovascular events by warmer weather/acute heat-waves may be more acute. For example, heat stress may rapidly provoke cardiac arrhythmias and cardiac arrest due the cascade effect of excessive sweating leading to a combination of hypotension and electrolyte imbalance [37].

Traditionally, seasonal vulnerability has not been identified as an important therapeutic target. Subsequently, there has been little effort from a clinical management perspective to attenuate its deleterious effects. However, considering that it is likely underpinned, at least in part, by adverse interactions between environmental and, bio-behavioural factors in vulnerable patients, it is highly plausible that this phenomenon can be addressed at the individual level. Critically, as reflected by our findings, this phenomenon persists among those exposed to evidence-based management specifically designed (and proven) to minimise recurrent hospitalisation and premature mortality [11]. This is most probably due to a combination of three interrelated factors – 1) these programmes are facing an increasing proportion of patients with vulnerability to seasonality (multimorbidity being a

critical factor in this regard); 2) they are not specifically geared to recognise and respond to individual seasonal vulnerability from a clinical perspective; and 3) an increasing frequence in extreme climatic events [38]. It is on this basis that we have previously identified the need to develop multi-faceted interventions specifically designed to identify high-risk/vulnerable patients and promote their resilience to seasonal change/acute weather events. [6] Avoiding high exertion activities such as shovelling snow in the more extreme climates [39], applying greater protection from the cold via housing design and clothing [40], maintaining appropriate physical activity levels during winter, or avoiding exposure to high levels of air pollutants or smoke haze [41, 42], are all examples of measures that may increase the resilience to, or reduce the influence of, environmental provocations in high-risk populations. Individual behaviour, however, is not simply a function of intention and awareness of the likely consequences of action/inaction, but the capacity to implement change through financial means/resources [43, 44]. Therefore, future research should develop and test a globally applicable health care program that aims to provide the necessary resources to an at-risk individual, which may improve their seasonal resilience.

A number of limitations must be considered when interpreting the findings of this study. Firstly, it was undertaken on a retrospective basis and provides important, but not definitive insights into this phenomenon. For example, it might be argued that the phenomenon we observed reflects a secondary cluster of readmissions typically occurring within 30-90 days amongst the sickest of patients. However, this does not explain why seasonality occurs on a *de novo* as well as recurrent basis, and study follow-up captured repeated exposure to seasons. We plan to address the potentially complex issue of prospectively identifying seasonally vulnerable individuals in future studies. These will specifically focus on the bio-behavioural and environmental factors (from the individual to

the broader climatic conditions) that drive vulnerability and, conversely, resilience to clinical instability on a seasonal basis. The subsequent development of valid and reliable seasonal risk score is entirely feasible on this basis. [6] Consistent with past studies identifying the role of meteorologic conditions in provoking cardiovascular events [6], comprehensive studies of seasonality from a clinical perspective need to capture such data. By necessity, we required patients to be exposed to all four seasons to reveal a pattern of seasonality and examined outcomes on a rudimentary monthly/seasonal basis rather than a continuous/actual climatic conditions basis.

In conclusion, this study found clear evidence of seasonality in a real-world cohort of older patients initially admitted to hospital with chronic heart disease. Overall, we found that more than one in four patients had multiple readmissions associated with a prolonged hospital stay in one particular season. Distinctive patterns in respect to the demographic, clinical and bio-behavioural profile of such "seasonal frequent flyers" suggest that vulnerability to seasonality should be recognised as a clinical phenomenon that can be both identified and then optimally managed to prevent recurrent hospitalisation and premature mortality. Pending further research to definitively phenotype seasonality (thereby resulting in an agreed definition), these data should strongly encourage clinicians to carefully consider their patient's vulnerability during characteristically cold or warmer parts of the year and/or the random occurrence of extreme climatic conditions; the importance of air quality and background levels of viral infections being important considerations in this regard. Likewise, they should consider practical advice (e.g. avoiding physical exertion during cold-snaps and/or prioritising household heating) and interventions (e.g. influenza vaccination and/or modifying diuretic therapy during heatwaves) to promote seasonal resilience in otherwise vulnerable individuals.

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Table 1 Baseline characteristics of the entire cohort (n=1598) and according to season of index admission

	ALL (n=1598)	Summer (n=338)	Autumn (n=429)	Winter (n=429)	Spring (n=402)
Socio-demographic profile					
Female	624 (39%)	122 (36%)	164 (38%)	166 (39%)	172 (43%)
Age (years)	70 (12)	70 (12)	70 (12)	71 (12)	71 (12)
Living alone	686 (43%)	145 (43%)	186 (43%)	179 (42%)	176 (44%)
Less than 12 years education*	350/1581 (22%)	55/335 (16%)	97/426 (23%)	101/426 (24%)	97/394 (25%)
Low income status*	99/1595 (6%)	20/338 (6%)	21/427 (5%)	29/429 (7%)	29/401 (7%)
Behavioural profile					
Abdominal obesity*	610/1503 (41%)	123/310 (40%)	147/402 (37%)	172/406 (42%)	168/385 (44%)
Meeting exercise guidelines*	604/1589 (38%)	127/335 (38%)	174/425 (41%)	158/428 (37%)	145/401 (36%)
Current smoker	274 (17%)	63 (19%)	73 (17%)	71 (17%)	67 (17%)
High-risk alcohol use	238 (15%)	41 (12%)	70 (16%)	68 (16%)	59 (15%)
Total cholesterol ≥ 4.0 mmol/L*	384/793 (48%)	82/175 (47%)	115/230 (50%)	101/203 (50%)	86/185 (46%)
Clinical presentation					
Systolic Blood Pressure (mmHg)*	134 (24)	132 (24)	135 (23)	135 (24)	132 (23)
Diastolic Blood Pressure (mmHg)*	75 (15)	75 (15)	77 (15)	76 (15)	73 (14)
Heart rate (beats/min)*	85 (27)	84 (26)	83 (26)	86 (27)	86 (27)
Left ventricular ejection fraction*	47 (17)	46 (16)	48 (17)	48 (17)	47 (17)
Grip strength (kg) *	20 (10)	21 (11)	22 (10)	20 (11)	21 (11)
Hba1c (%)*	6.6 (1.5)	6.7 (1.7)	6.5 (1.4)	6.7 (1.4)	6.7 (1.4)
Renal failure (eGFR<60mls/min/1.73m^2)*	622/1553 (40%)	130/327 (40%)	137/411 (33%)	176/419 (42%)	179/396 (45%)
Anaemia (sex-specific)*	617/1551 (40%)	124/326 (38%)	153/414 (37%)	170/415 (41%)	170/396 (43%)
Mild cognitive impairment*	676/1258 (54%)	157/279 (56%)	159/328 (48%)	180/320 (56%)	180/331 (54%)
Depressive symptoms*	271/995 (27%)	61/227 (27%)	81/286 (28%)	68/258 (26%)	61/224 (27%)
Clinical profile					
Type 2 diabetes	557 (35%)	124 (37%)	139 (32%)	143 (33%)	151 (38%)
Charlson Comorbidity Score	5.7 (2.7)	5.7 (2.6)	5.4 (2.7)	5.8 (2.9)	5.9 (2.5)
Coronary artery disease	931 (58%)	196 (58%)	252 (59%)	244 (57%)	239 (59%)
Heart Failure	861 (54%)	176 (52%)	197 (46%)	243 (57%)	245 (61%)
Atrial Fibrillation	803 (50%)	169 (50%)	179 (42%)	225 (52%)	230 (57%)
Respiratory disease	287 (18%)	64 (19%)	72 (17%)	80 (19%)	71 (18%)
In-hospital management at index admission					
Median length of stay	5 (3-9)	5 (3-9)	5.0 (3.0-10.0)	5 (3-9)	5 (3-8)
Coronary revascularisation	442 (28%)	101 (30%)	123 (29%)	118 (28%)	100 (25%)
Primary Discharge Diagnosis*					
Acute coronary syndrome	22/989 (2%)	6/225 (4%)	4/286 (1%)	6/258 (2%)	6/220 (3%)

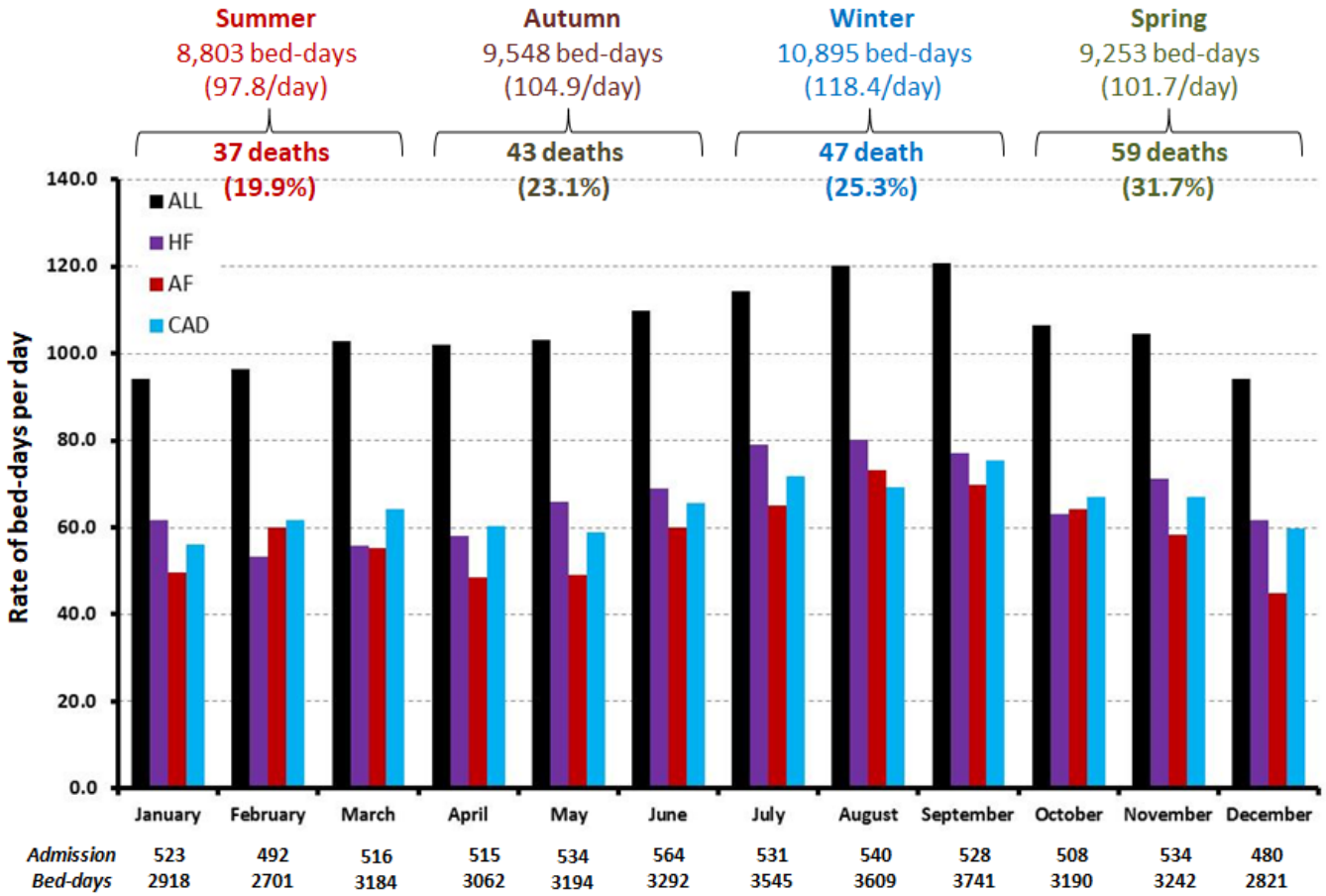
Acute heart failure	150/989 (15%)	33/225 (15%)	37/286 (13%)	42/258 (16%)	38/220 (17%)
Stable coronary artery disease	296/989 (30%)	66/225 (29%)	94/286 (33%)	78/258 (30%)	58/220 (26%)
Atrial Fibrillation	186 /989 (19%)	42/225 (19%)	38/286 (13%)	58/258 (22%)	48/220 (22%)
Cerebrovascular disease	18/989 (2%)	6/225 (3%)	4/286 (1%)	3/258 (1%)	5/220 (2%)
Other cardiovascular	31 /989 (3%)	8/225 (4%)	8/286 (3%)	10/258 (4%)	5/220 (2%)
Non-cardiovascular	286 /989 (29%)	64/225 (28%)	101/286 (35%)	60/258 (23%)	61/220 (28%)
Discharge pharmacotherapy					
ACEi	786 (49%)	175 (52%)	196 (46%)	214 (50%)	201 (50%)
ARBs	376 (24%)	78 (23%)	111 (26%)	102 (24%)	85 (21%)
β-blocker	1015 (64%)	216 (64%)	260 (61%)	280 (65%)	259 (64%)
Diuretic	907 (57%)	184 (54%)	207 (48%)	255 (59%)	261 (65%)
Nitrate therapy	529 (33%)	108 (32%)	128 (30%)	146 (34%)	147 (37%)
Anti-arrhythmic agent	251 (16%)	56 (17%)	75 (17%)	57 (13%)	63 (16%)
Anti-platelet/Anti-coagulant	1218 (76%)	245 (72%)	337 (79%)	335 (78%)	301 (75%)

Data are presented as mean (SD), median (IQR), or number of patients (%). Depressive symptoms determined by positive response to two-item Arroll tool[27] and mild cognitive impairment score ≤ 26 on the Montreal Cognitive Assessment (MoCA) tool.[28] ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; eGFR, estimated glomerular filtration rate. *Data not available for all patients.

Table 2. Pattern of seasonality in patients with at least one readmission during follow-up (n=1,158)

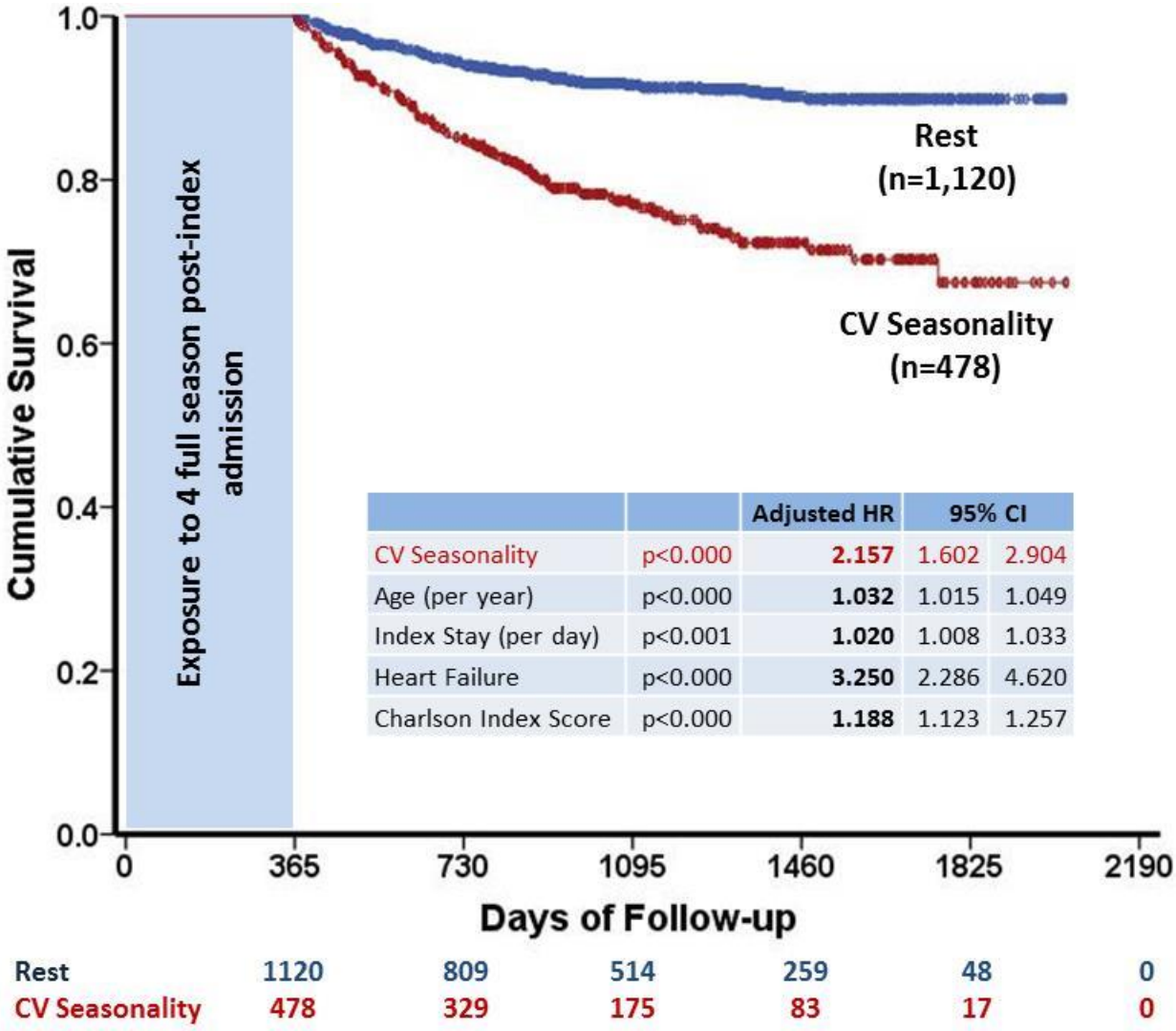
	SUMMER		AUTUMN		WINTER		SPRING	
ALL (N=1,158)	1,411 admissions	7,950 days	1,436 admissions	8,371 days	1,528 admissions	9,591 days	1,450 admissions	9,380 days
No Seasonality n=680 (59%)	646 (45.8%)	3,335 (41.9%)	684 (45.8%)	3,939 (41.9%)	707 (46.2%)	4,343 (45.2%)	639 (44.1%)	4127 (44.0%)
Summer Seasonality n=107 (9.2%)	324 (22.9%)	2,517 (31.7%)	123 (8.6%)	465 (5.6%)	120 (7.9%)	415 (4.3%)	122 (8.4%)	487 (5.2%)
Autumn Seasonality n=110 (9.5%)	138 (9.8%)	519 (6.5%)	312 (21.7%)	2617 (31.3%)	147 (9.6%)	567 (5.9%)	132 (9.1%)	534 (5.7%)
Winter Seasonality n=128 (11.1%)	145 (10.2%)	666 (8.4%)	158 (11.0%)	637 (7.6%)	361 (23.6%)	3318 (34.6%)	159 (11.0%)	597 (6.4%)
Spring Seasonality n=117 (10.1%)	147 (10.4%)	627 (7.9%)	136 (9.5%)	559 (6.7%)	177 (11.6%)	749 (7.8%)	370 (25.5%)	3436 (36.6%)
Dual Seasonality n=16 (1.4%)	11 (0.8%)	86 (1.1%)	23 (1.6%)	154 (1.8%)	16 (1.1%)	109 (1.1%)	28 (1.9%)	199 (2.1%)

Figure 1. **Pattern of hospital stay and all-cause mortality according to month and season**



Legend: Rates of hospital stay (bed-days per day of the month) are adjusted for the number of days per month and individual contributions to all-cause admissions (BLACK BARS) activity levels are counted once (n=1598). Figures for HF (PURPLE BARS), AF (RED BARS) and CAD (BLUE BARS) are based on diagnosis at index discharge (patients with multiple diagnoses can contribute to two or three categories).

Figure 2. **Long-term survival profile (Kaplan-Meier Curves) according to presence versus absence of seasonality**



Legend: Box insert shows the results of a Cox-Proportional Hazards Model.