ABSTRACT

Background: The stability of the new GOLD 2017 COPD staging is unknown, as well as the frequency of individual transitions in COPD stages beyond one year.

Methods: All COPD participants in the CHAIN cohort were re-analysed according to GOLD 2017 up to five years of follow-up. Their individual changes within COPD stages were aggregated into cohort-wide Markov chains; group stability was evaluated using joinpoint regression.

Results: At baseline, 959 COPD patients were distributed according to GOLD 2017 stages as 37.7% in A, 38.3% B, 8.2% C, and 15.7% D. The group proportion of patients in each stage was maintained from years one to five. However, we found significant changes between stages at the individual patient level, especially in the more severe stages. The probability of a patient remaining in the same GOLD 2017 COPD stage for two consecutive years ranged during the five years of follow-up for stage C from 16% to 31% per year, while for D from 23% to 43% per year, indicating substantial variation either increasing or decreasing severity for the vast majority of patients.

Conclusions: We conclude that group stability observed in COPD staging according to GOLD 2017 recommendations is paired with a large variability at the individual patient level.

Keywords: COPD; GOLD 2017; Markov chains; Severity; Staging

Trial registration number: NCT01122758

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health problem and will remain a challenge for the foreseeable future.[1,2] Yet, the diagnosing and staging of COPD have been controversial and without universal agreement.

On November 16, 2016 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) initiative modified its global COPD recommendations.[3] GOLD greatly simplified the COPD severity staging recommendations, now based on symptoms and history of exacerbations exclusively, and not including FEV_1 as before GOLD 2017 (**Table 1**).[4]

The prospective validity of this new GOLD 2017 staging has been independently validated by Gedebjerg, A, et al.,[5] and Cabrera-López C, et al.[6] However, the stability of the new GOLD 2017 COPD staging is unknown, as well as the frequency of the individual transitions in COPD severity beyond one year. This is most relevant considering renewed interest in the natural history of COPD,[7] when old concepts on progression of COPD have been challenged with new evidence coming from population cohorts[8] and clinical patients.[9,10]

Previously, our group characterized the GOLD 2015 staging, concluding that a change in GOLD 2015 category after one year was associated with longitudinal changes in the CAT and BODE index.[11] However, new analytical tools might help to represent the likely many trajectories occurring in longer periods of follow-up. A Markov chain is a model describing a sequence of possible events in which the probability of each event depends only on the state attained in the previous event.[12] They have found extensive application in Medicine.[13,14]

Considering all the above,[15] we aimed to determine the longer-term distribution (longer than one year and up to five years) of the new GOLD 2017 COPD stage transitions.

METHODS

We analyzed data from the COPD History Assessment In SpaiN (CHAIN) study,[16] a multicenter, observational, prospective cohort of COPD patients from 24 university, public hospitals in Spain, who are monitored annually (ClinicalTrials.gov Identifier: NCT01122758).

Details on recruitment and methodology of the CHAIN cohort have been published elsewhere[16]. COPD was defined by smoking history ≥10 pack-years and a post-bronchodilator FEV_1/FVC <0.7 after 400 µg of inhaled salbutamol. At baseline, all patients were stable for at least 8 weeks and received optimal medical therapy. Briefly, CHAIN participants were initially followed-up during a 5-year study period with complete office visits every 12 months and telephone interviews every 6 months in order to evaluate exacerbations and their life status. The recruitment period was between 15 January 2010 and 31 March 2012. At each annual visit, information was collected. Data were anonymized in a database with a hierarchical access control in order to guarantee secure information access.

All COPD participants in the CHAIN cohort were analysed according to GOLD 2017 up to five years of follow-up, up to December 6, 2017. A Markov chain model was created from data and analysed with the R-language for statistical computing.[17]

Statistical methods

We evaluated trends in the proportion of patients for each group in the GOLD 2017 classification by fitting a generalized linear model with a logit link function and a binomial distribution.[18] The significance of regression parameters was established using $P < 0.05$. To determine breakpoints we performed joinpoint regression.[19] Basically, a joinpoint is a systematic, independent way to identify significant breaks in the temporal distribution and trends of any given variable.[20] Significance in all estimates was established if the 95% confidence intervals of the regression parameters did not include zero. We modelled the transitions of patients between groups by using a discrete time in-homogeneous Markov chain.[21] We estimated the transition probabilities between groups for each year using the maximum likelihood method. We used for the analysis R version 3.4.3 to perform parameter estimation and regression, the package igraph,[22] for visualizing the transition probabilities of the Markov Chain, and the package segmented for joinpoint regression.[23]

RESULTS

We investigated 959 COPD patients with a mean±SD age of 66.3±9.7 years, 19% female and 33.3% still current smokers, with a cumulative smoking of 54.6±28.3 pack-years. At baseline, their severity was distributed according to GOLD 2017 stages as 362 (37.7%) in A, 367 (38.3%) B, 79 (8.2%) C, and 151 (15.7%) D (**Table 2**). After a relative change to milder severities in the first year, the relative percentage distribution was maintained from years one to five of follow-up (**Figure 1**). Quantitatively, there was a joinpoint in stages A at 2.3 years and B at 3 years (both $p<0.001$), followed by a strong negative relationship from each up to year 5 (both $p<0.05$); no significant joinpoints were observed for stage C, with a strong negative relationship all the way up to year 5 (both $p<0.001$); finally, there was an initial significant negative trend in the stage D ($p<0.001$), a joinpoint at 2 years, and then a positive relationship ($p<0.05$).

Although the proportions of all stages remained largely stable in the overall population after the baseline assessment (from A being the most frequent, to B, D, and then C as the least frequent) (**Figure 1**), there were significant changes between stages at the individual patient level, especially for the more severe stages, where patients in stages C and D only remained 22% and 31% for any two consecutive years within the same stage (**Figure 2**). This pooled variation within GOLD 2017 COPD stages during the five years of follow-up identified many combinatorial changes out from a total maximum of 4^6, that is combinations with order and repetition of four stages (A to D) during six points in time (baseline and five years). Within any possible 4.096 options, a total of 432 sequences were observed. That means that nearly half (432/939=45.0%) of patients had a unique trajectory just within the four GOLD 2017 stages. Within those CHAIN participants without any missing staging, the three most frequent trajectories were: first: AAAAAA (that is consistently stage A from baseline and all

five assessments) observed in 47 (4.9%) of patients; second: BBBBBB in 17 (1.8%) of patients.; and third: CAAAAA in 8 (0.8%) of patients. Note that these three Markov chains only accounted for 7.5% of all trajectories, further exemplifying a myriad of individual patient trajectories. On the contrary, the least common were DDDDCC, DDDDDB, and DDDDDD with one (0.1%) each.

In fact, the year-by-year variation within GOLD 2017 COPD stages during five years of follow-up for repeats of stage C ranged from 16% to 31% per year, while for D ranged from 23% to 43% per year (**Figure 3**). The Markov transition B → A was slightly more likely within the first year of follow-up. However, for C → A and for D → A there seemed to be little change over the years. In particular, those patients in stage D, the most severe COPD patients, remained 31% of times in D, ranging from a low of 23% in transitions from year 1 to 2, up to a high of 43% in year 3 to 4.

As per guidance by the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) initiaitive (https://www.strobe-statement.org/, in **Table 3** you can find a non-response survey comparing characteristics at baseline of those CHAIN participants who completed all five years of follow-up (n=366) versus non-completers (n=593). At baseline, non-completers were 2.6 years older, had a greater CAT score (12.3±7.6 vs. 10.7±7.2), and had more frequently mMRC dyspnea ≥2 (45.7% vs. 34.2%), all with $p<0.05$. However, these statistically significant differences are of relatively moderate nominal value, and there were no statistically significant differences in all other demographic and clinical comparisons at baseline. Therefore, the representativity of the final sample is confirmed.

DISCUSSION

Within a large, well-defined, clinical series of COPD patients followed up to five years, we report that, after a change to milder severities in the first year, their relative percent distribution was sustained. The group stability observed in the COPD severity staging was paired with a large variability of staging at the individual patient level. Of interest, severity was not modified in one in three COPD patients in GOLD 2017 D.

Although there are many reports presenting the distribution of several iterations of the GOLD staging at baseline in different populations and settings,[24] only a handful have reproduced longitudinal changes. Our group reported the one-year variation of GOLD 2011,[11] which included lung function, identifying an association with longitudinal changes in the CAT and BODE index; of interest, 71.5% of COPD D patients repeated staging one year after entry, which in retrospect represents more stability than with GOLD 2017; a likely reason is that it is very difficult (almost clinically impossible) that any individual with ≤50 %predicted FEV_1 changes to anything higher than 50%. Counterintuitively, by removing spirometry in staging from GOLD 2015, it makes more likely that patients change their COPD severity. Also, the ECLIPSE group studied further old GOLD 2011 stages up to three years of follow-up, and helped to better delineate the heterogeneity, both cross-sectional and longitudinally, of the C and D GOLD subgroups.[25]

For further clinical interpretation, the Markov transition B → A is slightly more likely within the first year of follow-up. This could mean that any medical intervention after entering the cohort is effective. However, for C → A and for D → A there seems to be little change over the years. Whether these changes are related to regression to the mean, or to baseline patient characteristics, or are due to respiratory treatments or management of comorbidities, remain to be explored. Current COPD interventions, pharmacological or non-pharmacological, maybe insufficient given that 31% of those in GOLD stage D, that is nearly one in three of the most severe COPD patients, remained 31% of times in D at every transition probability. Future research should combine more studies on the natural history of COPD,[15] with new staging recommendations using evidence-based thresholds and variables.[26]

There are a number of strengths in our study, including novelty, size, and length of follow-up. Further, patients represent well the full range of COPD patients seen in a universal, free for all health system.[27,28,29,30,31] Also, our graphical representation with a sophisticated Markov methodology is within the first in clinical research. However, a number of limitations must be noted: Ours is an observational study cohort, and apart from individualised management of their COPD and other conditions, it is non-interventional. Therefore, many determinants may have had a role on the observed transitions of COPD stages, including smoking cessation and changes in frequency and type of smoking, adherence/variations in COPD pharmacotherapy during follow-up, other medications, development and changes in comorbidities, and else; further, given the 5-year duration, size of the cohort shrunk due to patients lost to follow-up, ending up with 366 patients, or 38.2% from onset; intrinsic to CHAIN, is that more than 80% of our COPD cohort is made of men, which represents the reality in our environment, although COPD has progressively been more “feminised” in other countries already;[32] given the natural history of COPD, pairing large underdiagnosis and misdiagnosis rates, with a high lethality, any follow-up of COPD patients likely suffers of the clinicians’s fallacy,[33] from the so-called “iceberg phenomenon”, a metaphor emphasizing that for most COPD the number of known cases of disease is outweighed by those that remain undiscovered.[34] This produces an inaccurate view of the nature and causes of a disease from studying the minority of cases of the disease that are seen in clinical treatment. This is further compounded when an illness maybe explained away by a sufferer as a “health problem that is not illness”, or these problems are seen as part of natural processes (e.g. aging) which may be aggravated by lifestyle (jobs, smoking, …) and are, by definition non-medical, such as smoker’s cough and COPD.

To construct the COPD stages by symptoms, any COPD CHAIN participant with either CAT≥10 or mMRC ≥2 were considered symptomatic. However, it is now known that both thresholds in mMRC or CAT might not be equivalent. For instance, an earlier CHAIN report concluded that CAT scores ≥ 17 provided a similar sensitivity than mMRC dyspnea scores ≥ 2 to predict all-cause mortality.[28] In a later pooled analysis of 41 cohorts and 18,000+ patients, the equivalence the equivalence was with CAT scores ≥ 18.[35] This a new call for action for GOLD to establish evidence-based COPD definitions, for staging as well as for treatment in their future iterations.

We conclude that the group stability observed in the COPD staging according to GOLD 2017 recommendations is paired with a large variability of severity staging at the individual patient level, which is observed up to five years of follow-up.

SUMMARY CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest to disclose in relation with this manuscript.

DISCLOSURES

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JBS is the guarantor of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data
MH performed the statistics and takes responsibility for the accuracy of the data analysis.
JBS, MH, CS and CC wrote the first draft of the manuscript.
All authors but JBS, MH and CS recruited participants and collected all medical information.
All authors contributed substantially to the interpretation and the writing of the manuscript, and approved its final version.
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The authors declare there are no conflicts of interest to disclose in relation with this manuscript. The CHAIN study was funded by AstraZeneca Spain S.A.

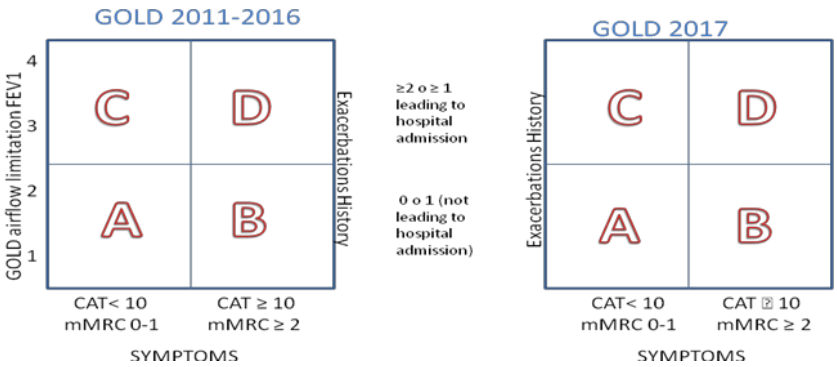
LIST OF FIGURES: (figures are in the attached PDF file "Figures Markov CHAIN.pdf")

Figure 1. Proportion of COPD patients in each GOLD 2017 COPD stage during five years of follow-up

Figure 2. Pooled variation within GOLD 2017 COPD stages during five years of follow-up

Figure 3. Year-by-year variation within GOLD 2017 COPD stages during five years of follow-up: 0 to 1 year, 1 to 2 years, 2 to 3 years, 3 to 4 years, and 4 to 5 years, respectively

Table 1. GOLD grading 2011 and 2017 recommendations to stage COPD



Footnote to Table 1: Airflow limitation thresholds of %predicted FEV_1: 1-mild: >80% ; 2-moderate: 50-80% ; 3-severe: 30-50% ; and 4-very severe: <30%.
mMRC : modified Medical Research Council questionnaire
CAT : COPD Assessment Test

Table 2. Demographic and clinical characteristics of CHAIN participants at baseline

Variable	Value
Age in years, mean±SD	66.3±9.7
Female, n (%)	183 (19.0)
Current smoker, n (%)	320 (33.3)
Pack-years, mean±SD	54.6±28.3
CAT score , mean±SD	12.1±7.2
mMRC dyspnea ≥2, n (%)	396 (41.2)
COPD exacerbations in the last 12 months, mean±SD	1.9±1.4
COPD hospitalizations in the last 12 months, mean±SD	1.4±0.8
GOLD 2017 stages, n (%)	
A	362 (37.7)
B	367 (38.3)
C	79 (8.2)
D	151 (15.7)
Number (%) of patients available during follow-up	
At baseline	959 (100.0)
Year 1	778 (81.1)
Year 2	658 (68.6)
Year 3	574 (59.9)
Year 4	471 (49.1)
Year 5	366 (38.2)

Table 3. Non-response survey comparing characteristics at baseline of CHAIN Completers (n=366) and Non-completers (n=593)

Variable	Non-completers (n=593)	Completers (n=366)	P value
Age in years, mean±SD	67.3±9.9	64.7±8.9	<0.001
Female, n (%)	108 (18.2)	75 (20.5)	0.398
Current smoker, n (%)	207 (34.9)	113 (30.9)	0.205
Pack-years, mean±SD	54.3±28.5	55.1±27.9	0.638
CAT score , mean±SD	12.3±7.6	10.7±7.2	<0.001
mMRC dyspnea ≥2, n (%)	271 (45.7)	125 (34.2)	<0.001
COPD hospitalizations in the last 12 months, mean±SD	1.5±1.0	1.2±0.5	0.155
GOLD 2017 stages, n (%)			0.094
A	210 (35.4)	152 (41.5)	
B	241 (40.6)	126 (34.4)	
C	44 (7.4)	35 (9.6)	
D	98 (16.5)	53 (14.5)	

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Figure 1

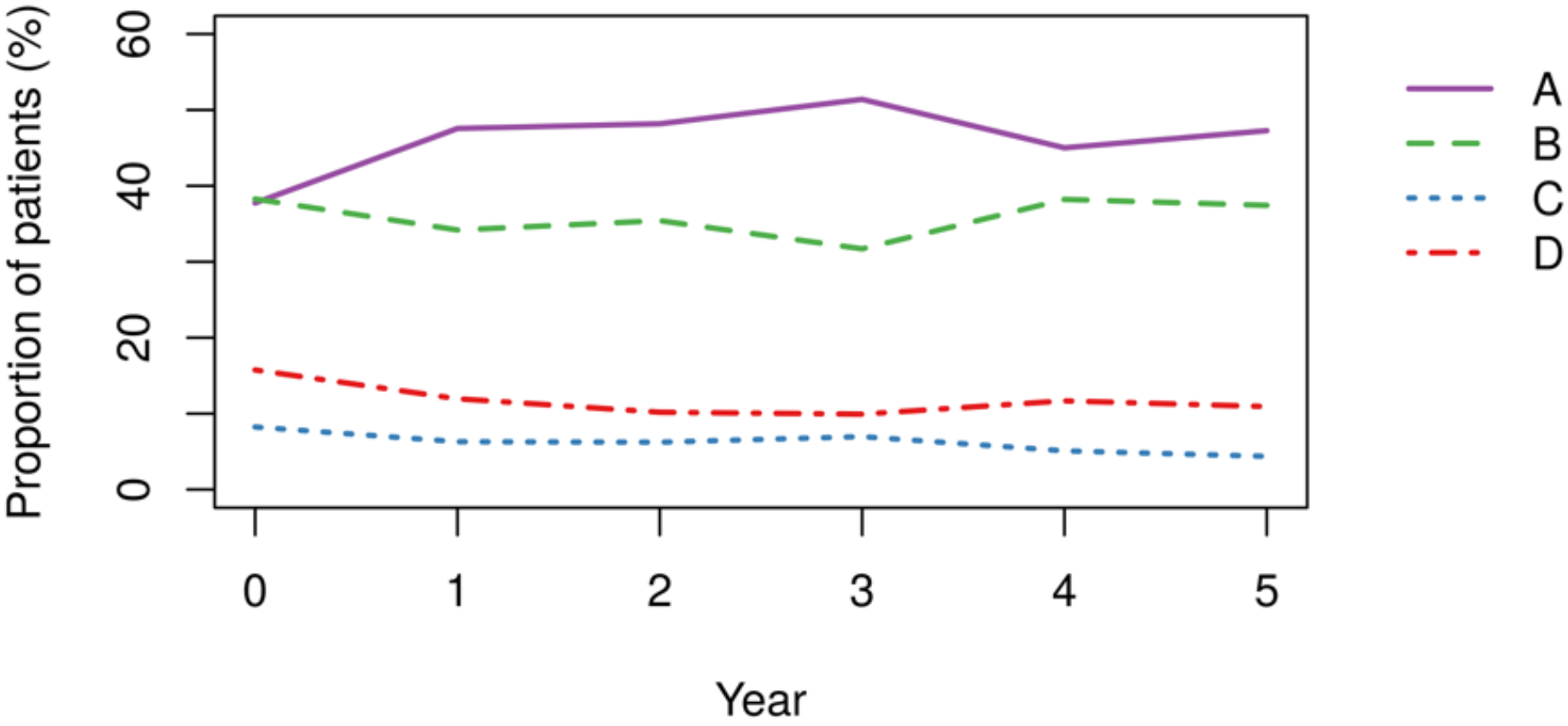
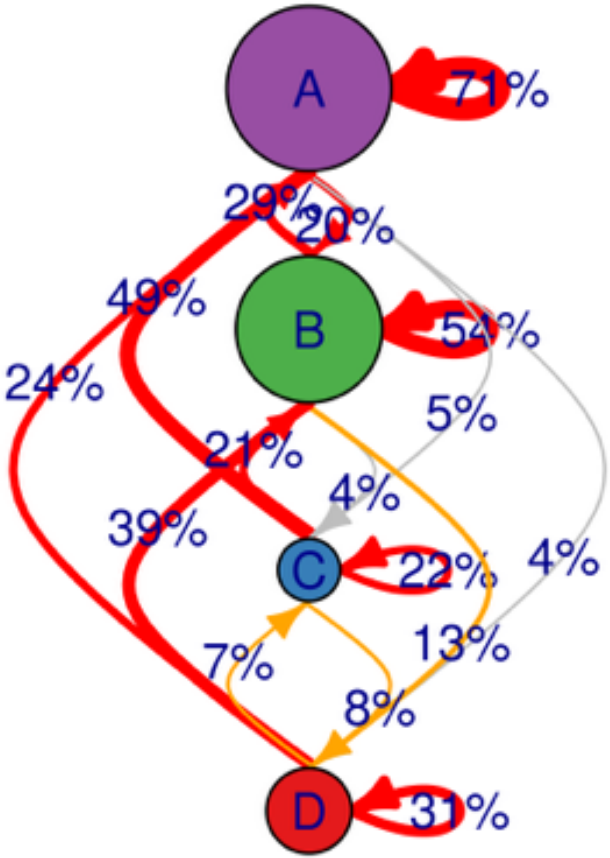
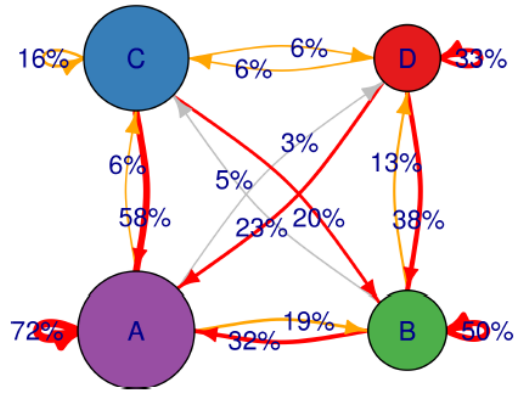


Figure 2

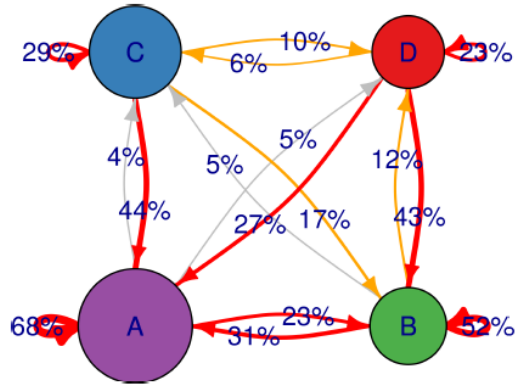


Figure

3a) Year 0 to 1



3b) Year 1 to 2



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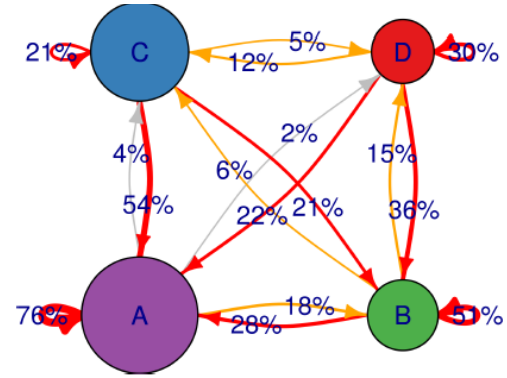
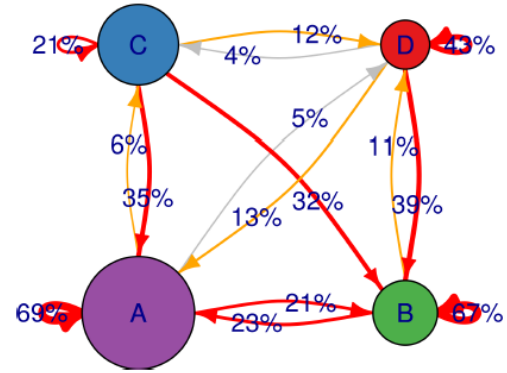


3d) Year 3 to 4



3e) Year 4 to 5